# Tenosynovial Giant Cell Tumours

## The good, the bad and the ugly

Floortje G. M. Verspoor

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# Tenosynovial Giant Cell Tumours

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**Dedicated to**
**Cornelis Bernards Theodorus Verspoor**
1922-2000

# Contents

# 1

# General introduction

## Terminology

Tenosynovial giant cell tumours (TGCTs) are a rare family of proliferative and inflammatory diseases.[1] They are benign, usually mono-articular lesions arising from the synovium, bursae and tendon sheaths, and present either as a single nodule (localised) or as multiple noduli (diffuse).[2] Clinically, TGCTs can exhibit a range of behaviours, from favourable to locally aggressive, and can consequently have a major impact on daily life.[3-6]

The disease was first described in 1852 by the French surgeon M. Chassaignac, who overstated the biological potential of the tumour by referring to it as 'a cancer of the tendon sheath'.[7] The first generally accepted clinical description was published in 1941 by H. L. Jaffe et al.,[2] who reported 20 cases with joint and tendon involvement and proposed a classification using location and histology.

The histopathological, clinical and radiological definition of TGCT remained undefined for decades, with many different names for the same entity used interchangeably. The nomenclature outlined by Granowitz et al.[8] in 1976 was modified by the World Health Organization (WHO) in 2002, and was used to classify giant-cell containing tumours by their origin; bone, soft tissue, synovium and tendon sheath. The two known subtypes, localised and diffuse, were renamed by the WHO; 'localised pigmented villonodular synovitis (PVNS)' was changed to 'giant cell tumour of the tendon sheath (GCT-TS)' and 'diffuse PVNS' became 'diffuse-type giant cell tumour (Dt-GCT)'.[9] In 2013, the denomination was adjusted again, and TGCT was suggested to replace both names.[1] Within the localised TGCTs, a distinction was made between TGCT affecting digits and TGCT occurring in and around larger joints.[10,11] Currently, there is still disagreement on the nomenclature of these diseases, and a new WHO classification is in preparation. In clinical practice, the 'PVNS' terminology is still used to maintain a clear distinction between giant cell tumours of the soft tissues (TGCT) and giant cell tumours of the bone, whereas pathologists and researchers use the most recently available WHO classification from 2013, which distinguishes localised- and diffuse-type TGCTs.[1]

An international multidisciplinary agreement on disease terminology and classification is important to ensure the reproducibility of diagnostic criteria, which would enable more accurate predictions about the biological potential of the tumour as well as facilitate the development of customised treatment regimens. Adequate and standardised disease names/terminologies, including meaningful classifications, will also make TGCT research more comparable and reliable.

## Aetiology of pathogenesis

For more than a century, the pathogenesis of TGCT has been poorly understood. Numerous hypotheses were studied, including neoplastic, inflammatory, traumatic, metabolic and viral pathways, but none of them could be confirmed as the causal mechanism.[8] In recent years, TGCT was found to be a clonal process associated with specific genetic changes, frequently due to a specific translocation: t(1;2) CSF-1:COL6A3*. Typically, a reactive component was also involved, causing the proliferation and recruitment of colony-stimulating factor 1 receptor (CSF-1R)-expressing cells such as macrophages, giant cells and osteoclasts. This is known as the 'paracrine landscape effect',[12-14] a concept which could lead to the development of new targeted treatment strategies. Targeted therapies are beneficial because they specifically block the growth of tumour cells by interfering with molecules needed for carcinogenesis and tumour growth, rather than by simply interfering with all rapidly dividing cells as is the case for traditional treatments such as chemotherapy.[15,16]

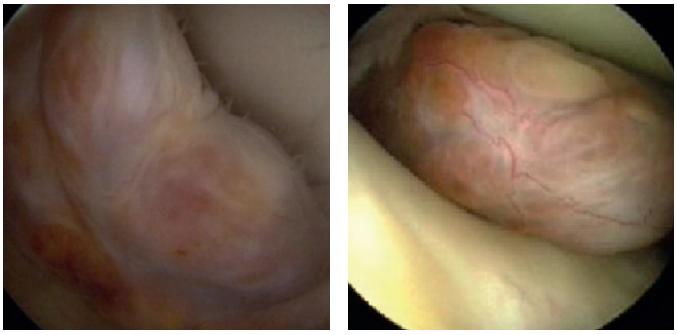
## Epidemiology

TGCT affects adults predominantly between 20 and 50 years of age, with equal sex prevalence.[1,5] The overall annual incidence has been estimated at 11 cases per million US inhabitants, including 9.2 localised and 1.8 diffuse cases per million.[4] This incidence is low, not only because of its rarity but likely because of the consequential unfamiliarity of doctors with the disease, which would probably lead to the underreporting and underdiagnosing of TGCT. Due to the chronic character of the disease, the prevalence should be much higher than was previously estimated; Ehrenstein et al. reported a prevalence of 44.3 and 11.5 per 100,000 people for localised- and diffuse-type TGCT, respectively.[17] Of the large weight-bearing joints, the knee is most often involved, followed by the hip, ankle, shoulder and elbow.[2,4,18]

## Clinical presentation

The diagnosis of TGCT can be difficult because of the variety of clinical symptoms, age and history of the patients, which means diagnosis is often delayed.[3,4] The disease mimics many other mono-articular pathologies due to the non-specific nature of its symptoms. Localised TGCT can present with locking or clicking sensations of the affected joint,[4,8] while the diffuse disease is relatively painless,

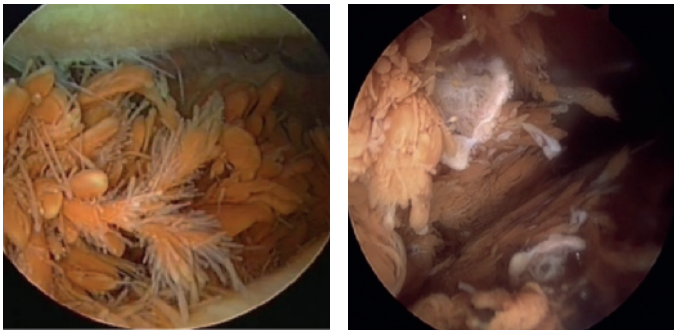
**Figure 1** Arthroscopy of the knee joint demonstrates localised-type TGCT.



Nodular lesion at the synovial lining of the anterior knee compartment.
Source: left, courtesy of www.boneschool.com by Dr. T. Dwyer; right, Loriaut et al.[22]

although it can cause discomfort and swelling.[3,4] Patients can also present with stiffness or a limited range of motion, and haemorrhagic effusions are common.[19] At the time of initial diagnosis, the symptoms have often been present for a long time, sometimes even years.[3,4] Patient complaints may increase as the disease progresses and becomes disabling, with a negative impact on daily life and activities; however, the exact impact is difficult to quantify because very little research exists on this topic.[6,20,21]

**Figure 2** Intra-operative arthroscopic pictures of diffuse-type TGCT.



Both pictures demonstrate the brown or reddish synovial proliferation typical for diffuse- type TGCT. The image on the right demonstrates a mirror view of the diffuse-type TGCT on a femoral prosthesis.
Source: left Mohanlal et al.[24]; right, Chen et al. [25]

In patients with knee complaints who undergo an arthroscopy, TGCT may be recognised because of its macroscopic features.[23] Localised TGCT is well circumscribed and typically lobulated (figure 1), and is white to grey with yellowish and brown areas. Diffuse-type TGCT is often a large (> 5 cm) firm or sponge-like yellow-brownish lesion (figure 2). The typical villous pattern (for which it was previously named pigmented villonodular synovitis) is usually lacking in extra-articular tumours.[1]

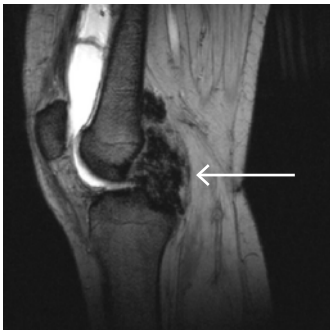
Very rarely, patients with diffuse-type TGCT develop metastatic disease, initially mostly pulmonary metastases, which are ultimately fatal.[26] Remarkably, this aggressive stage can present with inflammatory symptoms, such as fever, sweating, anorexia and weight loss, which might be caused by cytokines.[26-28] The pattern of synovial gene expression and protein activities in TGCT is similar to those in the activated macrophages in rheumatoid arthritis, while the phenotype of multinucleated giant cells, characteristic of the osteoclasts, suggests that there is a common autocrine mechanism in both diseases that might indicate the potential utility of a tumour necrosis factor (TNF)-alpha blockade.[29] The systemic effect of the cytokines and their role in the inflammatory symptoms of TGCT requires further research.

## Diagnosis

Previously, the diagnosis of TGCT was solely based on histopathology; however, magnetic resonance imaging (MRI) is now commonly used for the diagnosis, staging and follow-up evaluations of the disease.[30-32] Haemosiderin deposition occurs in the majority of TGCT cases and is most prominent in the diffuse intra-articular form of the disease (figure 3).[30] Haemosiderin is an iron-storage complex deposited in proliferative synovial tissues, resulting in spotty or extensive low-signal areas in T1- and T2-weighted images that can be best seen on fast-field echo sequence MRI images.[33] These deposits, which are obscured by fat-suppressed sequences, are highly diagnostic of TGCT.[30]

In the localised disease, MRI reveals a conspicuous nodular proliferation of the synovium (figure 4). Diffuse-type TGCTs mostly present as poorly defined peri-articular villous masses, which are frequently associated with degenerative joint disease and cystic lesions in the adjacent bone (figure 5).[34] Currently the literature lacks specific MRI discriminating features by which to describe or quantify the tumour extent in relation to clinical outcome. The development of uniform MRI descriptions is therefore of the utmost importance for clinical and research purposes.

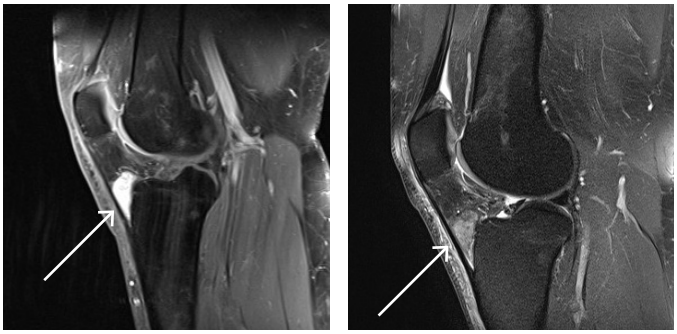
**Figure 3** Magnetic resonance imaging of recurrent diffuse-type TGCT with haemosiderin deposition.



Sagittal $T_2$-weighted MR image shows recurrent villous proliferation of the posterior compartment of the left knee with haemosiderin deposition (arrow).

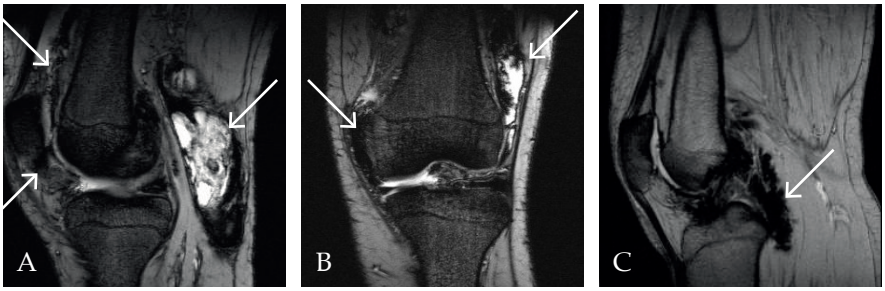
Histopathologically, localised- and diffuse-type TGCT are indistinguishable;[35] their microscopic appearances are variable, depending on the proportion of mononuclear cells (mainly small histiocytic-like cells), multinucleate giant cells, foamy macrophages, siderophages and the amount of stroma (figure 6). Haemosiderin deposits are always present (figure 7), and the stroma shows variable degrees of hyalinisation.[1] Cleft-like spaces are less frequently observed in localised-type than diffuse-type TGCTs.[1]

**Figure 4** Magnetic resonance imaging of localised-type TGCT in a left knee.



Sagittal view $T_1$-weighted turbo spin echo images. The fat-saturated (left) and proton-density (right) sequences show a nodular lesion at the synovial lining of the anterior knee compartment (arrow).

**Figure 5** Magnetic resonance imaging of diffuse-type TGCT.




Left knee: sagittal (**A**) and coronal (**B**) T2-weighted images show extensive intra- and extra-articular villous proliferation of the synovium (arrow). Right knee: sagittal (**C**) T2-weighted images show extensive villous proliferation of, in particular, the posterior compartment with haemosiderin deposition (arrows).

## Treatment

Little progress has been made in the treatment of TGCT, particularly for the diffuse subtype.[11,36] To date, surgical resection is the primary treatment for both subtypes (figure 8); however, despite being a generally benign neoplasm, diffuse-type TGCT can behave aggressively at a local level and is challenging to remove completely.[37,38] The pathologic tissue is widely spread, surrounding vital structures such as the cruciate ligaments, collateral ligaments, menisci, and rarely even infiltrating the neurovascular bundle.[39,40] Residual disease is therefore often accepted to spare these structures, which are of vitally importance for joint function and stability.[36] Surgery often requires one or multiple synovectomies, in certain cases a joint

**Figure 6** TGCT histological samples depicting mononucleated and some multinucleated giant cells and the inflammatory reaction (haematoxylin and eosin stain).

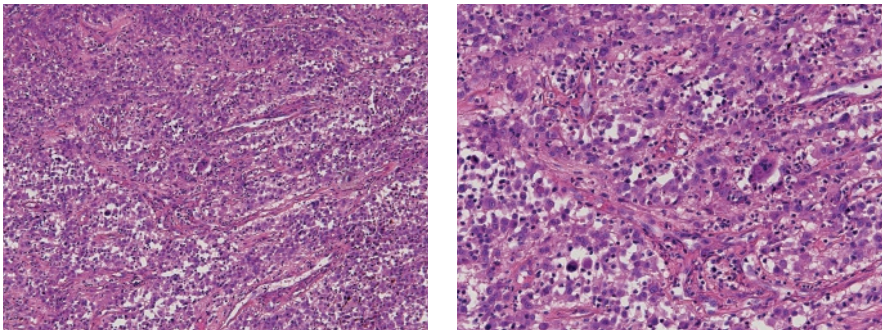
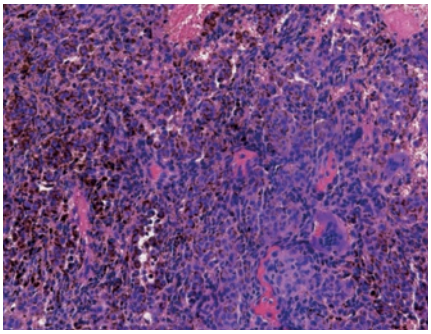


**Figure 7** TGCT histological sample demonstrating brown granular deposits of haemosiderin (haematoxylin and eosin stain).

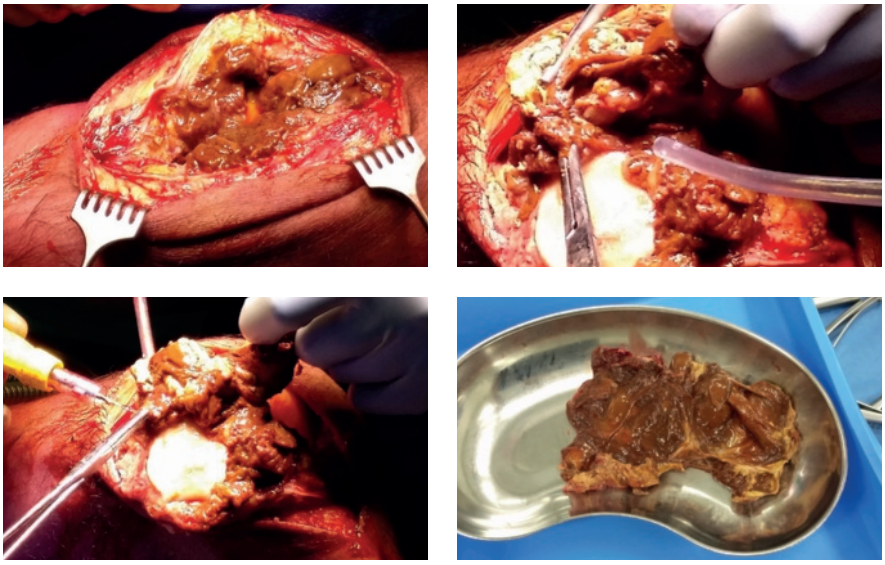


replacement, and in exceptional cases even amputation.[41-43] In these exceptional aggressive cases, there is invasive growth in the bone and soft tissue. Amputation follows a process of multiple treatments for extensive disease or is the final resort after (major) complications, for example peri-prosthetic infections.[43]

For diffuse-type TGCTs there is little consensus about the most appropriate type of surgery. Both arthroscopic and open surgical excisions are commonly used, and the synovectomies can either be partial or complete.[44,45] In patients with extensive and/or recurrent TGCT, other treatment modalities may include a radiation synovectomy,[46] external beam radiation therapy,[47] immunotherapy[48] and cryosurgery,[49] the effects of which are controversial.[3,19,50-59] No randomised controlled trials comparing these different treatments, including surgical resection, have been performed, meaning all available evidence is based on retrospective case series. These existing case series are difficult to compare because different disease locations, subtypes, and primary and recurrent TGCTs are grouped together to increase patient numbers,[11,51] while various outcome measures are used to assess the treatment success.[41,44,51,60]

In recent years, targeted therapy has been added to the armamentarium. Patients with extensive, recurrent or metastatic TGCTs were previously treated with imatinib or nilotinib, but currently more specific inhibitors of CSF-1R (figure 9), including emactuzumab (RG7155)[61] and cabiralizumab[62] (FPA008, Five-Prime), have shown promising clinical activity in patients with diffuse-type TGCT.[16, 63-65] Pexidartinib (PLX3397)[66], a selective inhibitor of CSF-1R, Kit (Kit receptor is a transmembrane protein), and FLT3-ITD (Fms-like Tyrosine Kinase 3- Internal Tandem Duplication), showed promising results in a randomised, placebo-controlled, phase 3 study.[63-65]

**Figure 8** Intra-operative pictures of an open surgical synovectomy of diffuse-type TGCT in the knee.

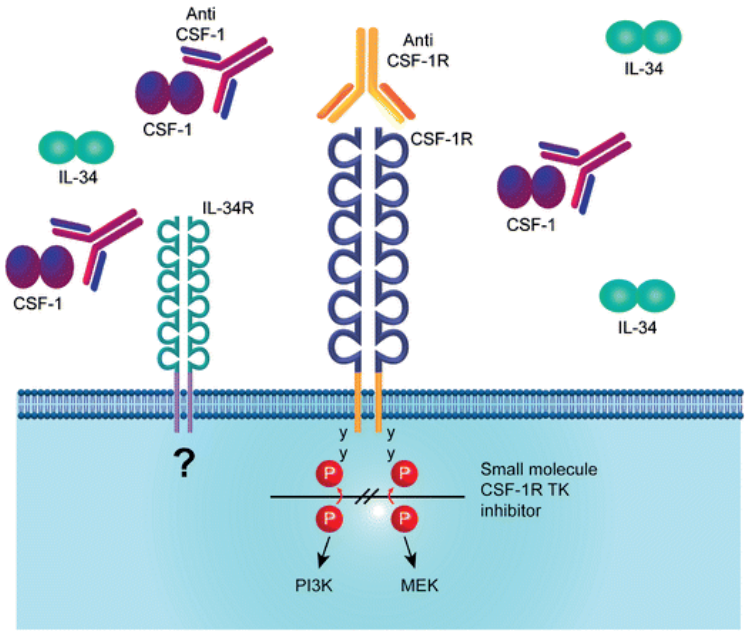


Intra-operative pictures of an open surgical synovectomy showing brown synovial proliferation of the anterior compartment of the knee caused by haemosiderin deposition typical of diffuse-type TGCT.

## Outcome

The surgical treatment for TGCT is guided by its clinical and radiological presentation. Localised-type TGCT comprises a single nodular or pedunculated lesion and has a favourable course, rarely recurring (10–15% recurrence) after marginal surgical excision.[3,19,41] The less common diffuse-type TGCT tends to be more aggressive and involves the synovial lining and the surrounding structures. It is associated with a significant risk of recurrence, ranging from 9% to 46% depending on the joint involved and the duration of follow up, and may result in a chronic disease, hampering the normal function of the affected joint.[1,3,50,68] In rare cases, diffuse-type TGCT is capable of malignant transformation;[26,30] there is no available information on the aetiology of this malignant transformation, no curative treatment is available, and the prognosis is dismal. The currently available targeted treatments do not have a documented effect on metastatic diffuse-type TGCT, and are given on a 'compassionate use' basis outside trials due to a lack of alternative treatments. Genomic alterations might influence the sensitivity of tumour cell to specific inhibitors of CSF-1R.[69,70] A very rare observation was a systemic effect from

**Figure 9** Mechanisms of action of the CSF-1R inhibitors[67].

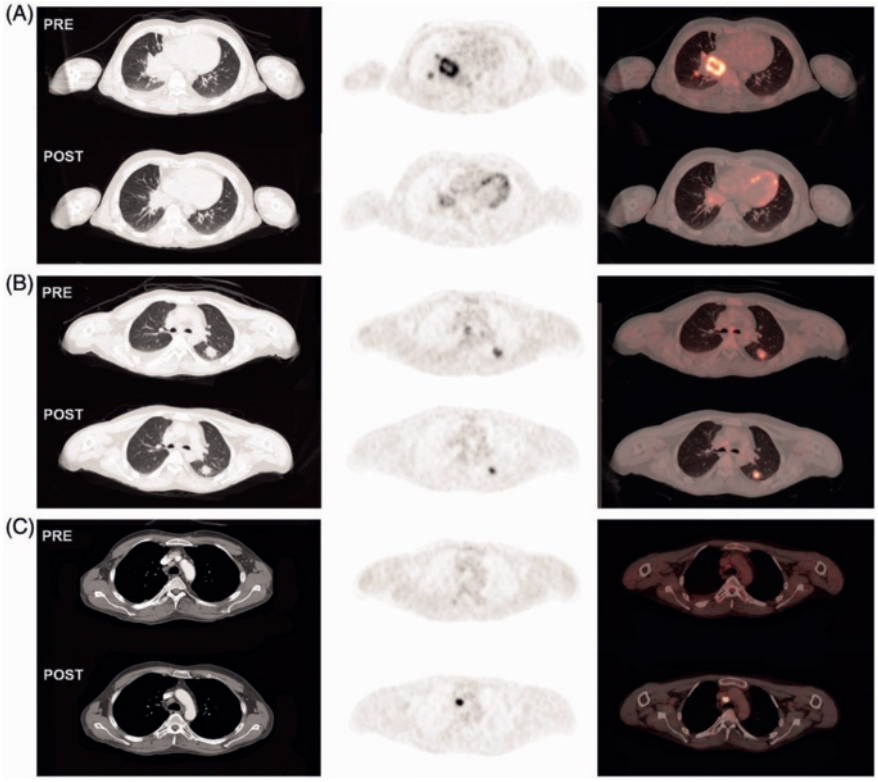



Intra-operative pictures of an open surgical synovectomy showing brown synovial proliferation of the anterior compartment of the knee caused by haemosiderin deposition typical of diffuse-type TGCT.

local radiotherapy resulting from an abscopal effect in a patient with metastatic diffuse type-TGCT, which resulted not only in a response in the right irradiated hilar lesion, but also in the left non-irradiated pulmonary metastasis (figure 10).[26]

The primary end point in oncologic clinical trials is often overall survival, but this is not appropriate for TGCT which is rarely lethal.[71] Alternate endpoints include response rates, progression free survival, and time without active treatment. Quality of life (QoL) and functional scores are of utmost importance, but mostly absent or described for small, heterogeneous patient groups.[20] These outcome measures demonstrate the clinical relevance and impact of treatments in patients with this benign chronic disease.[72]

**Figure 10** Abscopal effect of radiotherapy in a patient with metastatic diffuse-type TGCT.[26]




Computed tomography (CT, left column), FDG-positron emission tomography (PET, middle column), and combined FDG-PET-CT image (right column), before the start (pre) and after the completion (post) of radiotherapy. (a) High uptake of FDG in the right hilar diffuse-type TGCT metastasis before the start of radiotherapy with an impressive decrease in FDG-uptake three weeks after the completion of radiotherapy, corresponding with the metabolic response. (b, c) Abscopal effect in the left pulmonary metastases (b) and mediastinal lymphadenopathy (c), showing a volume response in the pulmonary lesions on the CT and a metabolic response on the FDG-PET-CT images, as well as an increased uptake in a mediastinal lymph node on FDG-PET-CT, in keeping with an immunological reaction.

## Aim and outline of this thesis

TGCT presents at a relatively young age and can have a major impact on life; however, most clinicians are not familiar with the disease and its consequences. Some patients with diffuse-type TGCT experience evident morbidity, as a result of the disease itself or its treatments. Despite these issues, the only available evidence is based on retrospective case series.

The aim of this thesis is to investigate the incidence, diagnosis, treatments and outcomes of patients with TGCT in large joints to enhance the quality and efficiency of diagnostics and treatments for patients affected by this (chronic) condition. Ultimately, this should lead to improvements in patient outcomes.

The only available data on the incidence of TGCTs were published in 1980[4] and the surprisingly low rates are likely to reflect the underreporting and underdiagnosis of this rare disease. **Chapters 2 and 3** present a nationwide incidence study, which was undertaken to map the true incidence of TGCT in adults and children. The characteristics of TGCT in children were compared with those of adults to define the similarities and differences, including in relation to the aggressiveness of the disease.

Using MRI, we can visualise the characteristic features of TGCT that enable the distinction between the localised and diffuse subtypes of the disease.[30] Clinically, patients present with a more or less aggressive diseases of a single subtype. In **chapter 4,** the objective MRI characteristics of TGCT are described, and a radiology-based severity classification for patients with TGCT in large joints is presented, enabling the objective differentiation between the severity stages of TGCT. This classification should enhance the information given to patients, provide insights into recurrence risk and improve personalised treatment regimens; for example, more aggressive disease types may require a different treatment regime than milder forms of the disease.

Several multimodal treatments have been applied in addition to or after surgical synovectomies in an attempt to reduce recurrences. In **chapter 5,** the broad spectrum of available treatments (e.g., surgery, radiation synovectomy, external beam radiation therapy and systemic treatments) is further explored, and their effects are evaluated in a systematic review of the literature. Based on this research, guidelines are formulated to support physicians in making optimal, consistent treatment plans for patients with TGCT.

Subsequently, the outcomes for subgroups of patients who receive these multimodal treatment(s) were retrospectively analysed. **Chapter 6** reports on the outcome of arthroplasty in the treatment of TGCT, while **chapter 7** describes cryosurgery in addition to a surgical synovectomy.

Another treatment option is imatinib mesylate. TGCTs are rare CSF-1-driven proliferative disorders, and one of the targets of imatinib mesylate is CSF-1R.[16] **Chapter 8** reports the results of an international, multicentre study on the long-term effects of treatment using imatinib mesylate in patients with TGCT, including the prolonged activity after discontinuation, as well as its safety.

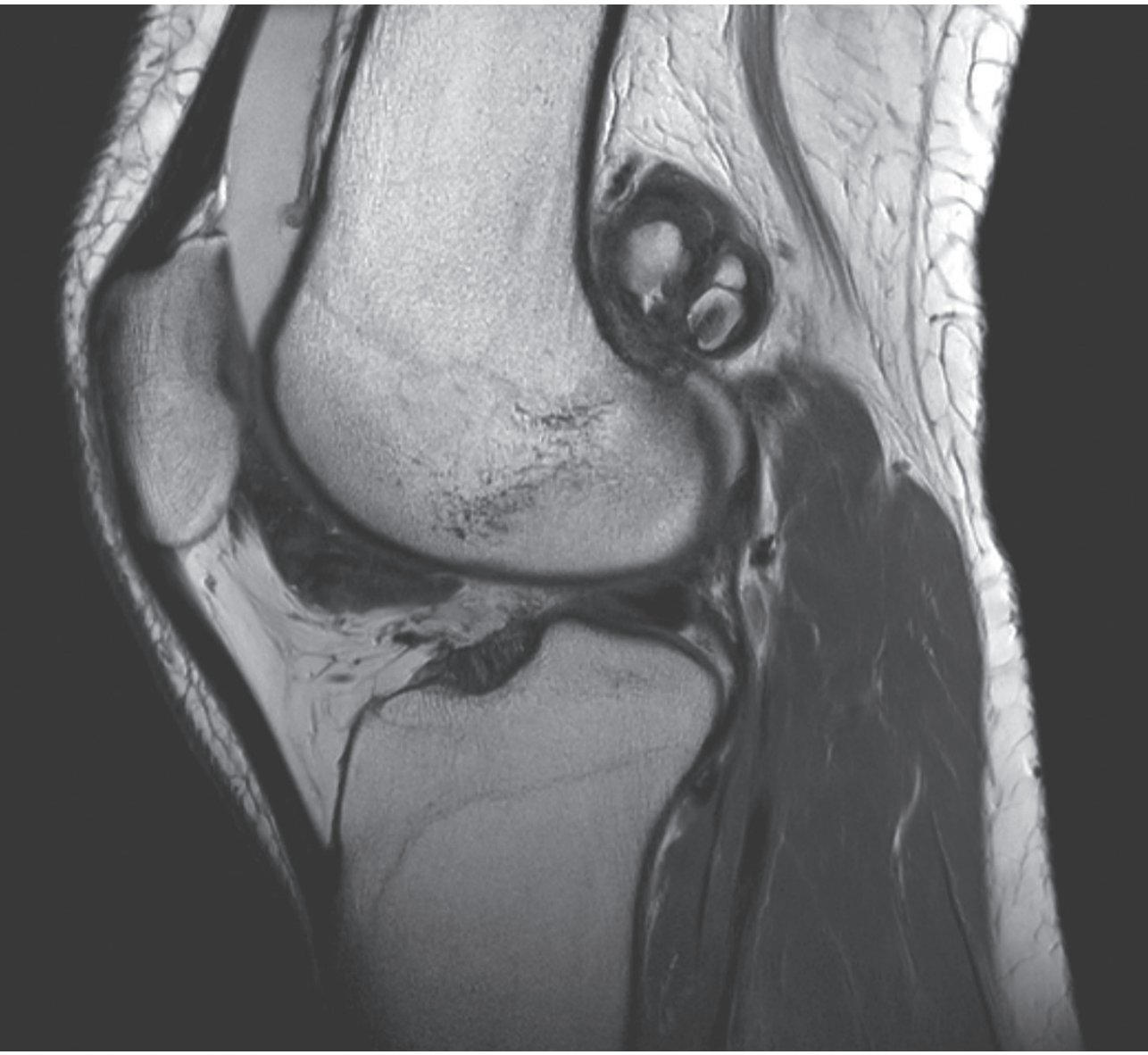
In **chapter 9,** the treatment effects of a very select subgroup of patients with TGCT in the temporomandibular joint are studied. TGCT in the temporomandibular joint is even less common than rare malignancies such as sarcomas or metastases.[73] The temporomandibular joint is a difficult location to treat due to its proximity to the brain and other vital structures. In cases of extensive or recurrent illness, TGCT in the temporomandibular joint cannot be radically treated with surgery alone. Other treatments, such as external beam radiation or target therapy, were provided to the patients, and the results of three new cases are reported in addition to a review of the existing literature.

Adequate documentation on the outcomes of TGCT treatment is lacking. Previous case studies have used relatively short follow-up times and often combine locations or disease subtypes to increase patient numbers. In **chapter 10,** the long-term outcomes of a large consecutive series of patients with TGCT are analysed. Overall survival is often the primary end point in oncologic clinical trials, but it is not appropriate for TGCT as the disease is rarely lethal.[71] Alternate endpoints include response rates, progression-free survival, and the avoidance of morbid therapies. Quality of life (QoL) and functional scores demonstrate the clinical relevance and impact of treatments in benign diseases, but are largely absent in TGCT research.[72] In **chapter 11,** pre- and post-operative patient-reported outcome measures (health-related QoL and joint function) are investigated in patients with TGCT.

In **chapters 12 and 13,** the results of this thesis are summarised and discussed. The thesis is concluded with future perspectives, including suggestions for further research using collaborative, better-organised and international approaches.

# 1

# Incidence



# 2

# Higher incidence rates than previously known in Tenosynovial Giant Cell Tumors

MJL Mastboom, FGM Verspoor, AJ Verschoor, D Uittenbogaard, B Nemeth, WJB Mastboom, JVMG Bovée, PDS Dijkstra, HWB Schreuder, H Gelderblom, MAJ van de Sande; TGCT study group.

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## Abstract

Tenosynovial giant cell tumors (TGCT) are rare, benign tumors, arising in synovial lining of joints, tendon sheaths, or bursae. 2 types are distinguished: localized, either digits or extremity, and diffuse lesions. Current TGCT incidence is based on 1 single US-county study in 1980, with an incidence of 9 and 2 per million person-years in localized (including digits) and diffuse TGCT, respectively. We aim to determine nationwide and worldwide incidence rates (IR) in TGCT affecting digits, localized-extremity TGCT and diffuse- type TGCT.

Over a 5-year period, the Dutch Pathology Registry (PALGA) identified 4,503 pathology reports on TGCT. Reports affecting digits were solely used for IR calculations. Reports affecting extremities were clinically evaluated. Dutch IRs were converted to world population IRs.

2,815 (68%) digits, 933 (23%) localized-extremity and 390 (9%) diffuse-type TGCT were identified. Dutch IR in digits, localized-extremity, and diffuse-type TGCT was 34, 11 and 5 per million person-years, respectively. All 3 groups showed a female predilection and highest number of new cases in age category 40–59 years. The knee joint was most often affected: localized-extremity (46%) and diffuse-type (64%) TGCT, mostly treated with open resection: localized (65%) and diffuse (49%). Reoperation rate due to local recurrence for localized-extremity was 9%, and diffuse TGCT 23%.

This first nationwide study and detailed analyses of IRs in TGCT estimated a worldwide IR in digits, localized-extremity and diffuse TGCT of 29, 10, and 4 per million person-years, respectively. Recurrence rate in diffuse type is 2.6 times higher, compared with localized extremity. TGCT is still considered a rare disease; however, it is more common than previously understood.

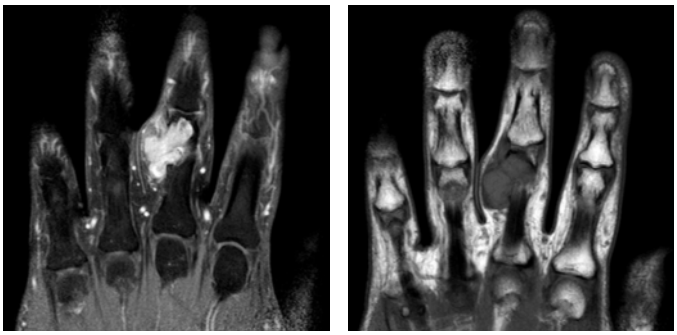
# Introduction

Tenosynovial giant cell tumors (TGCT) are a rare entity, affecting generally young patients (below the age of 40 years), with an equal sex distribution. The World Health Organization (WHO) classification of Tumors of Soft Tissue and Bone (2013) distinguishes 2 TGCT types: localized and diffuse lesions.[1] Microscopically the 2 types show no clear difference. However, on magnetic resonance imaging (MRI) discrimination between these types is made.[30]

The localized type was previously described as giant cell tumor of tendon sheath, nodular synovitis or localized pigmented villonodular synovitis (PVNS). The typical macroscopic aspect is a well circumscribed, small (about 0.5 to 4 centimeters) usually lobulated lesion, with white to grey, yellow and brown mottled areas[1]. Based on anatomical site of the localized-type tumor, differentiation is made into a group affecting digits and a group occurring in and around larger joints.[74,75] TGCT affecting digits is defined as a localization distal to metacarpal or metatarsal bones; localized-extremity TGCT is defined as all sites near joints proximal and including metacarpal and metatarsal joints.

In localized TGCT, most lesions are found in the digits of hands and feet (figure 1). The majority of these lesions arise from the tendon sheath and less frequently from synovial lining of digital joints. Common treatment is marginal excision.[76,77] A systematic review showed a recurrence rate of 15%, after an average follow-up of 37 to 79 months.[78]

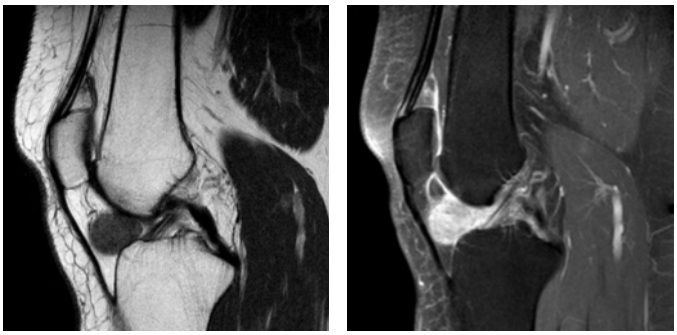
**Figure 1** MRI of localized-type TGCT, affecting digits.



A 43-year-old male patient with a well-circumscribed tumor in the proximal phalanx of the third digit of the right hand. Left panel: A coronal T1-weighted MRI after intravenous contrast injection. Right panel: A clear coronal T1-weighted MRI without intravenous contrast injection.

Fewer localized TGCT lesions are found around larger joints; they originate from synovial lining, tendon sheaths, or bursae (figure 2). The preferred treatment of these lesions is marginal excision by an arthroscopic or an open approach.[76,77] A systematic review reported an average recurrence rate of 6% after arthroscopic resection and 4% after open resection (with variable follow-up).[37]

**Figure 2** MRI of TGCT localized-type, extremity.



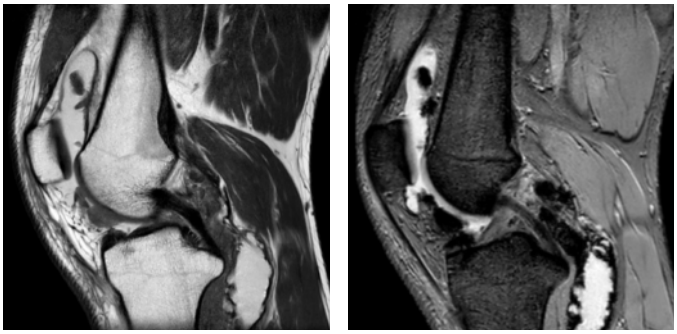
Sagittal T1-weighted turbo spin echo MRI of a 47-year-old female patient, affecting her right knee. A well-circumscribed lesion in Hoffa's fat pad is seen. Left panel: Proton density weighted MRI. Right panel: Pre-saturation inversion recovery MRI.

The diffuse-type TGCT, previously called diffuse pigmented villonodular synovitis (PVNS) or synovitis (villo)nodularis pigmentosa (SVP), is a more destructive and locally aggressive tumor (figure 3). Diffuse TGCT is defined by the presence of an infiltrative soft tissue mass along synovial lining, showing villous projections of the proliferated synovial membrane, with or without involvement of the adjacent joint or other structures. Macroscopically, the diffuse type affects a large part of synovial lining and has a multinodular, multi-colored appearance, including white, yellow and rust-colored areas[1]. 75% are located around the knee joint[37]. Current treatment is surgical excision.[76,77,79] However, it is often difficult to perform a marginal excision. Average recurrence rates after arthroscopy are 40% and after open resection 14%, with variable follow-up times.[37] In extensive disease, perioperative radiotherapy might reduce recurrence rate. [80,81] Patients with (multiple) recurrences experience impaired quality of life.[20]

According to the WHO classification of 2002 and 2013, the incidence rate (IR) in TGCT is not exactly.[1,82] Current TGCT IRs are based on 1 single US-county study completed in 1980, with an IR of 9 and 2 per million person-years in localized (including digits) and diffuse TGCT, respectively .[4] Verschoor and coworkers (personal communication 2015) performed the initial nationwide registry based

study on giant cell containing tumors and calculated an overall IR for TGCT of 50 per million per year. Discrimination between localized and diffuse disease was not possible as additional clinical information was lacking. The difference in biological behavior, however, demands further stratification of this general IR in the 3 different TGCT groups. Therefore, we aimed to estimate the worldwide (WHO standardized) TGCT IR by investigating clinical data of affected joints, sex differences, 10-year age-specific categories, initial treatments, follow-up, and recurrence rate at individual patient level through extensive additional data collection at participating hospitals.

**Figure 3** MRI of diffuse-type TGCT.



A 23-year-old male patient with an extensive proliferative synovial process around both cruciate ligaments, dominating the anterior and posterior knee compartments, intra- and extra-articular. Inside suprapatellar pouch and Baker's cyst a blooming villonodular aspect shows typical iron depositions. Left panel: Sagittal proton density weighted turbo spin echo MRI. Right panel: Sagittal T2-weighted fast field echo MRI.

## Material and methods

Data collection was performed by collaboration of physicians from the TGCT study group, and in special collaboration with Radboud University Medical Center and Medical Spectrum Twente, data collection was performed. Data capturing and analyses were performed in the Leiden University Medical Center.

A search in PALGA, the non-profit nationwide network and registry of histo- and cytopathology in The Netherlands, was performed (Casparie et al. 2007). To find all patients with TGCT, between January 2009 and January 2014, the search terms 'Tenosynovial Giant Cell Tumor', 'Pigmented Villonodular Synovitis' and a variety of synonyms were used, either as a code or as free text (Verschoor 2015, personal communication) (Appendix, see Supplementary data). Received pathology

reports provided limited and anonymous information on sex, age, date of tissue removal, and conclusion of the pathology report. In these reports, definitive diagnosis was frequently provided, but information on (localized/diffuse) type and affected joint was only sparsely available. Therefore, further investigation of additional clinical and radiological data was necessary. Reports with TGCT affecting digits were solely used for calculating incidence rate (for TGCT digits) and not further investigated clinically. PALGA interlinked 1,941 pathology reports to 95 Dutch hospitals of origin. Departments of pathology received a request to collaborate in this nationwide study. After approval, personal hospital identifiers were obtained and the departments concerned (mostly orthopedics and general surgery) were invited to confirm TGCT diagnosis and add detailed information on TGCT type, affected joint, sex, age at first histologically proven TGCT, primary treatment, total surgeries related to TGCT, date of last follow-up, and follow-up status. Clinical and radiographic data were derived from medical files. Data were kept anonymous. 75 of 95 attributed hospitals collaborated, including all specialized and academic centers.

Clinical evaluation started with1,941 eligible TGCT cases. In 1,576 (81%) cases, diagnosis was confirmed. 253 reports were determined to be in digits and amended in digits group. For included extremity TGCT cases (n = 1,323), incomplete evaluated clinical data were imputed for unknown data on TGCT type (n = 393), affected joint (n = 101), sex (n = 52), age (n = 54), and treatment (n = 484), using multiple imputation techniques. 10 datasets were imputed, and results were pooled according to standard Rubin's rules[83]. All imputed data were checked for errors.

Finally, 1,323 patients with histologically proven TGCT were included (figure 4).

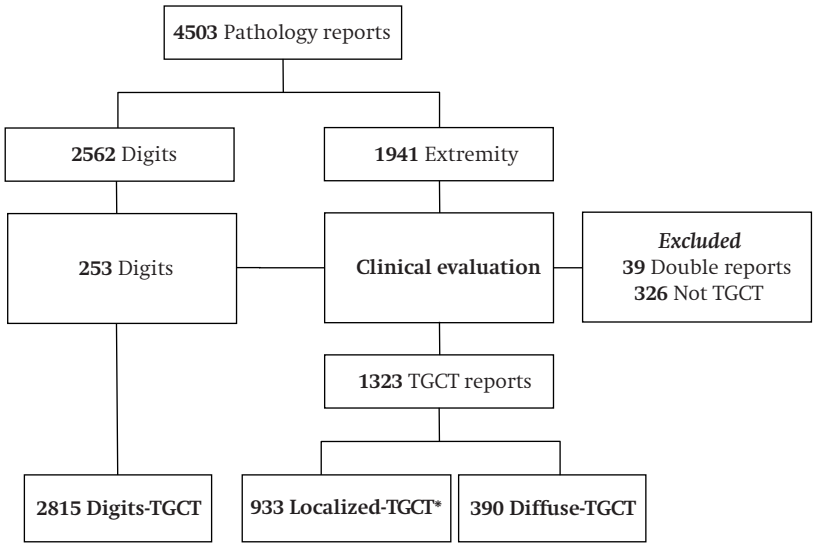
In addition to the 2,562 patients with TGCT affecting digits that were already identified based on the pathology reports, 253 additional patients with TGCT affecting digits were discovered during clinical data evaluation. 2,815 patients with TGCT affecting digits were identified (2,649 fingers, 119 toes, 47 finger or toe), but not investigated in detail.

Reoperation rate due to local recurrence was defined as surgery for recurrent TGCT, based on additional pathology reports in the same patient, at least 6 months after initial surgery until January 2015 (date of PALGA search).

## Statistics

The Statistical Package for Social Sciences statistics (SPSS®) version 23 (IBM Corp, Armonk, NY, USA) was used for analyses. The IR was separately estimated for localized TGCT, either digits or extremity, and diffuse-type TGCT per year, by using the number of histologically proven cases of TGCT as numerator and the sum of individual person-years for The Netherlands as the denominator. IRs were reported for the overall study period, by calendar year, and stratified on type,

**Figure 4** Inclusion flowchart.




[a] Localized TGCT affecting extremities, excluding digits.

affected joints, sex, and 10-year age categories (age at TGCT diagnosis). The Central Bureau of Statistics (CBS) provided information on Dutch population during the examined period. Overall worldwide IRs were obtained by standardizing Dutch IRs to global IRs by using the direct method, applying age-specific IRs in each 10-year age group to the world WHO standard population (http://seer.cancer.gov). Estimates of IRs were reported with 95% confidence intervals (CI). Patient demographics were reported as counts and percentages for categorical variables and as medians and interquartile ranges (IQR) for continuous variables.
The Kaplan–Meier method was used to evaluate reoperation due to local-recurrence-free survival at 2 and at 5 years.

## Ethics, funding, and potential conflicts of interest

Research was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. As this study does not involve subject-related research, it is not covered by Dutch law on human subjects research. The study was approved by the Institutional Review Board (CME) from our institution (registration number G16.024, 22 April 2016). No funding or benefits were received by any of the authors. There is no conflict of interest involving any of the authors.

# Results

During a 5-year period, 2,815 (68%) digits, 933 (23%) localized-extremity and 390 (9%) diffuse-type TGCT were identified. TGCT affected digits 3 and 7 times more often compared with localized-extremity and diffuse TGCT, respectively. Dutch TGCT IRs were 34 (CI 33–35) in TGCT affecting digits, 11 (CI 11–12) in localized-extremity TGCT and 5 (CI 4–5) in diffuse-type TGCT per million person-years. Median age for TGCT affecting digits was 49 (IQR 38–59) years, for localized-extremity TGCT 45 (IQR 34–56) years, and diffuse TGCT 47 (IQR 32–61) years. Male:female ratio was about 1:1.5 for any type.

**Table** Incidence rates (IRs) of localized and diffuse-type TGCT in The Netherlands.

| Person-years | | Localized TGCT: digits | | Localized TGCT: extremity | | Diffuse TGCT | |
|---|---|---|---|---|---|---|---|
| | | New [a] cases | IR [b] | New [a] cases | IR [b] | New [a] cases | IR [b] |
| Overall | 83,226,498 | 2,815 | 34 (33–35) | 933 | 11 (11–12) | 390 | 5 (4–5) |
| **Calendar year** | | | | | | | |
| 2009 | 16,485,787 | 578 | 35 (32–38) | 192 | 12 (10–13) | 73 | 4 (4–6) |
| 2010 | 16,574,989 | 561 | 34 (31–37) | 183 | 11 (10–13) | 82 | 5 (4–6) |
| 2011 | 16,655,799 | 580 | 35 (32–38) | 176 | 11 (9–12) | 78 | 5 (4–6) |
| 2012 | 16,730,348 | 563 | 34 (31–37) | 188 | 11 (10–13) | 77 | 5 (4–6) |
| 2013 | 16,779,575 | 533 | 32 (29–35) | 194 | 12 (10–13) | 80 | 5 (4–6) |
| **Sex** | | | | | | | |
| Female | 42,032,934 | 1,698 (60) | 40 (39–42) | 544 (58) | 13 (12–14) | 236 (61) | 6 (5–6) |
| Male | 41,193,564 | 1,117 (40) | 27 (26–29) | 389 (42) | 9 (9–10) | 154 (39) | 4 (3–4) |
| **Age at diagnosis** | | | | | | | |
| 0–9 | 9,528,271 | 13 (0) | 1 (1–2) | 6 (1) | 1 (0–1) | 2 (0) | 0 (0–1) |
| 10–19 | 10,012,994 | 98 (3) | 10 (8–12) | 57 (6) | 6 (4–7) | 26 (7) | 3 (2–4) |
| 20–29 | 10,178,289 | 259 (9) | 25 (23–29) | 108 (11) | 11 (9–13) | 49 (13) | 5 (4–6) |
| 30–39 | 10,673,194 | 411 (15) | 39 (35–42) | 169 (18) | 16 (14–18) | 62 (16) | 6 (5–7) |
| 40–49 | 12,894,743 | 650 (23) | 50 (47–54) | 211 (23) | 16 (14–19) | 70 (18) | 5 (4–7) |
| 50–59 | 11,456,662 | 704 (25) | 62 (57–66) | 193 (21) | 17 (15–19) | 71 (18) | 6 (5–8) |
| 60–69 | 9,466,681 | 503 (18) | 53 (49–58) | 133 (14) | 14 (12–17) | 58 (15) | 6 (5–8) |
| 70–79 | 5,680,080 | 155 (6) | 27 (23–32) | 41 (4) | 7 (5–10) | 37 (9) | 7 (5–9) |
| 80–89 | 2,860,556 | 22 (1) | 8 (5–12) | 15 (2) | 5 (3–9) | 15 (4) | 5 (3–9) |

Overall, by calendar year 2009–2013, sex and age categories.

[a] New cases: number of cases, %.

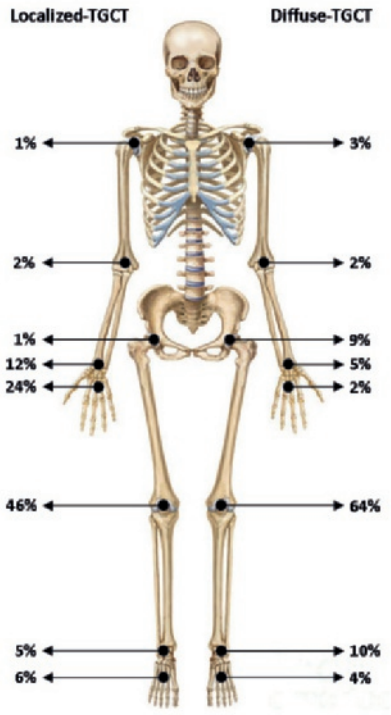
[b] IR = incidence rate per million person-years (95% CI).

The Table shows IRs per million person-years for calendar years 2009 up to and including 2013, sex, and 10-year age-specific categories of the 3 different TGCT groups. In these 3 groups: IRs over disaggregated years were quite similar, female IRs were slightly higher compared with male IRs, and the majority of new cases were seen in age categories 40–49 and 50–59 years.

In 2015, The Netherlands counted 16,900,726 inhabitants. According to calculated IR, 571 new TGCT affecting digits, 189 new localized-extremity and 79 new diffuse TGCT patients were diagnosed in 2015. The estimated standardized worldwide IRs were 29, 10, and 4 per million person-years for respectively localized-digits, localized-extremity and diffuse TGCT.

As TGCT affecting digits were not clinically investigated, the following results were based on localized-extremity and diffuse-type TGCT. The majority of TGCT cases affected the knee joint; 46% and 64% in localized and diffuse TGCT, respectively (Figure 5), followed by the hand and wrist joint in localized-type and

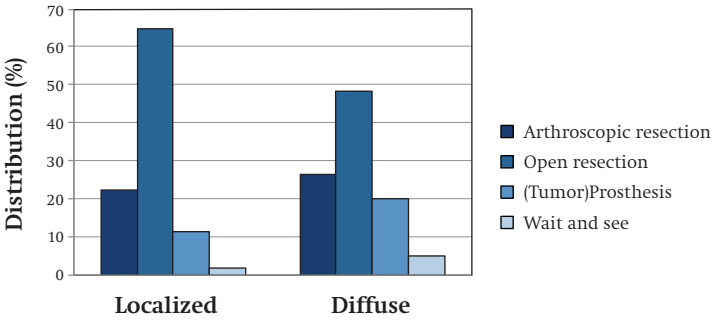
**Figure 5** Skeleton, showing affected TGCT localization (fingers and toes excluded).




3% in localized type and 1% in diffuse type is classified as “other”.

the ankle and hip joint in diffuse-type TGCT. Sex distribution per affected joint was comparable. The initial TGCT treatment plan was open resection in 65% and 49% in localized and diffuse lesions, respectively (Figure 6). TGCT was reported as an incidental finding during endoprosthetic replacement in 60 procedures.

**Figure 6** Initial treatment for TGCT affecting extremities in The Netherlands, excluding digits.

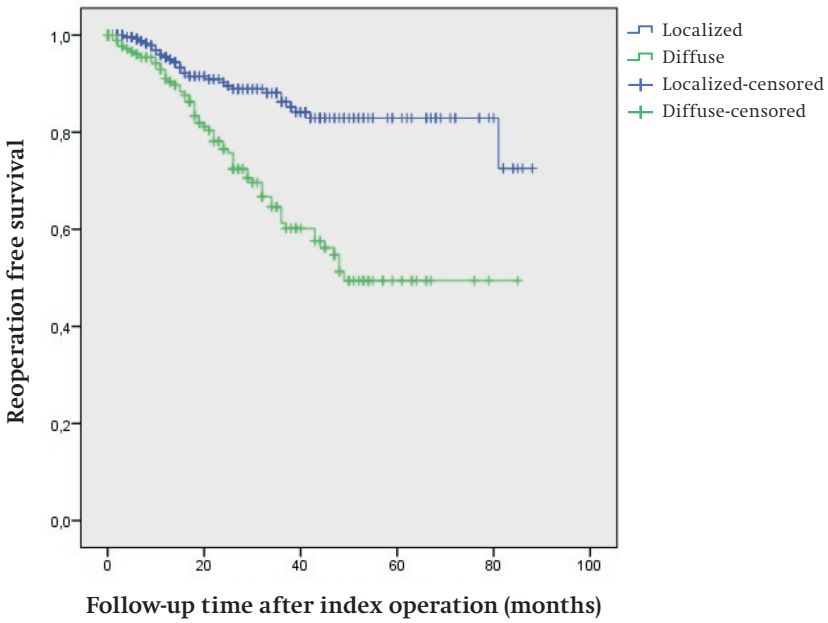



According to the clinical charts, the majority of patients were lost to follow-up in both types (71% in localized and 55% in diffuse TGCT). Therefore, we decided to base recurrence rates on additional surgeries (defined by a second pathology report documenting recurrence of TGCT in PALGA). By evaluating the municipal personal records database (Gemeentelijke Basis Administratie (GBA)) for all patients, 8 patients (7 localized and 1 diffuse TGCT) were deceased at time of evaluation and were censored at time of death when no second surgery was performed.

Reoperation rate due to local recurrence, calculated as a percentage from all TGCT patients, in localized TGCT was 9% and in diffuse TGCT 23%. Reoperation-free survival curves for localized and diffuse TGCT are shown in Figure 7. In the localized-extremity type, reoperation-free survival at 2 and at 5 years was 90% and 83%, respectively. In the diffuse type, reoperation-free survival at 2 and at 5 years was 77% and 49%, respectively.

Only a minority (12%) of TGCT patients were primarily treated in a tertiary oncology center: 9% of localized type (excluding digits) and 18% of diffuse type.

**Figure 7** Reoperation due to local recurrence-free survival curve in localized- extremity and diffuse TGCT (Kaplan-Meier), excluding digits.




Time zero is time of primary surgery. 8 patients died and were censored at time of death if a recurrence had not occurred.

## Discussion

Microscopically, localized-extremity and diffuse TGCT are identical.[1] A distinction is made between localized-digits and localized-extremity TGCT, based on anatomical location and histological differences.[74,75]. TGCT lesions affecting digits are characterized as multiple, small (average 1 centimeter) nodules surrounded by a thin fibrous capsule, originating in synovial tissue of tendon sheaths or small joints of digits, with a small number of cleft-like spaces and thick bundles of collagenous tissue, rarely showing inflammatory cells. Conversely, localized-extremity TGCT are typically single, relatively large (average 2 centimeters) lesions covered by 1 or more layers of synovial cells, intra-articular, showing large or numerous pseudo-glandular spaces sometimes filled with foam cells and showing more inflammatory cells than digits.[74]

Because of the rarity of the disease, the current TGCT literature contains predominantly retrospective, relatively small cohort studies, including hetero-

geneous data.[75] Two previous studies described TGCT incidence: Myers and Masi (1980)[4] reported 117 new cases of localized (including digits) and 49 new cases of diffuse-type TGCT between 1960 and 1976, resulting in an IR of 9 per million person-years for localized and 2 per million person-years for diffuse-type TGCT. A single hospital study was performed by Monaghan et al. (2001)[84] and showed an IR of 20 new cases per million per year between 1990 and 1997 for localized-type TGCT (including digits). Compared with the initial US-county study[4], our study showed a 5-fold higher IR in localized TGCT (combining localized-digits and localized-extremity), and a more than 2.6-fold higher IR in diffuse-type TGCT. This difference could be attributed to our nationwide coverage, our registry-based clinically verified character and because of increased knowledge about the disease.

Localized and diffuse lesions are distinguished clinically and on MRI. To investigate these lesions separately, clinical and radiological confirmation is of utmost importance. Treatment in localized TGCT affecting digits or extremity is mostly 1 single excision. In contrast, multiple mutilating surgeries are often required for diffuse-type TGCT, with a continuous risk of recurrences. In an effort to find all TGCT patients, our search included specific pathology codes for TGCT and both TGCT and synonyms of TGCT as free text (appendix). Therefore, cases with "synovitis" or differential diagnostic TGCT were also represented in our search. In addition, PALGA data are based on input of physicians and sometimes lack specificity. For instance, affected joint: "upper extremity", "hand", or "wrist" could all turn out, after clinical evaluation, to be affected digits.

In our search, 1,941 patients were clinically evaluated and 1,323 ascertained histologically proven TGCT extremity cases were included. Consequently, only 68% of eligible TGCT patients had histologically proven TGCT of the large joints. Without clinical TGCT confirmation, the estimated IR would have been much higher.

Despite our large number of patients with lack of follow-up, reoperation rates due to local recurrence were described, based on additional surgeries, defined by a second pathology report documenting recurrence of TGCT in PALGA (up to January 2015, the date when the PALGA search was performed). Recurrences without treatment (no additional pathology report) were not included, therefore reoperation rate due to recurrence is not identical to recurrence rate. However, compared with the literature, we found comparable average recurrence rates for localized-extremity TGCT (9%) and for diffuse-type TGCT (23%).[37] As local recurrence might develop years after initial surgery[42], and PALGA provided pathology reports with a maximum time of 7 years after initial surgery, underestimation of the true recurrence-free survival is likely.

There are some limitations to this study. Determined IR may be exposed to under- or overestimation. Primarily, our calculated IR could be slightly under-

estimated, because our study is based on a search in PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands.[85] TGCT patients without a biopsy or treatment are not represented in this pathology-based cohort. Second, our IR in localized-extremity and diffuse-type TGCT could be marginally over- or underestimated, because 21% of eligible TGCT patients were not clinically evaluated and were therefore imputed. Analyses with and without imputed data were comparable. PALGA identified 1,941 eligible TGCT patients, scattered over 95 Dutch hospitals. Regarding different hospital boards, the different departments concerned (pathology, orthopedics, general surgery), and different local legislation, it was challenging to evaluate all eligible TGCT patients.

Third, a clinical distinction between localized-extremity and diffuse-type TGCT is difficult, especially for clinicians not familiar with this rare disease.[86]

Subsequently, an overestimation of IR in localized-digits TGCT might be present. IR of digits is based solely on PALGA registry numbers, in contrast to localized-extremity and diffuse TGCT IRs, which were clinically evaluated.

Global IR were estimated by using a direct standardization approach (http://seer.cancer.gov). Even though this is a widely accepted method, there is no adjustment for other influences in global structure or possible risk factors in TGCT.

To calculate prevalence rates, follow-up time and status are important. The majority of our investigated patients lacked clinical chart follow-up. It seemed unfair to estimate TGCT prevalence rates as the proportion of TGCT patients alive at the end of 2013 and diagnosed with TGCT: this assumes TGCT not to resolve and not to be cured.

In The Netherlands, traditionally, larger orthopedic clinics have been treating TGCT or have diagnosed TGCT as an incidental finding during arthroscopy or endoprosthetic replacement. When (severe) complaints occur, patients are commonly referred to specialized tertiary sarcoma centers. In this study, we investigated primary patients to calculate incidence rate. No centralization of care of TGCT in these primary patients is shown, with only a minority of 12% primarily treated in a tertiary oncology center. Remarkably, only 18% of diffuse TGCT was primarily treated in tertiary oncology centers.

In summary, this study is the first nationwide study and the first to offer detailed analyses of IRs in TGCT. IRs for TGCT of digits, localized-extremity and diffuse-type were calculated using additional hospital record evaluation of patients originally selected from a nationwide pathology registry. The worldwide estimated incidence rate in digits, localized-extremity, and diffuse TGCT is 29, 10, and 4 per million person-years, respectively. Despite high clinical variability in localized-extremity and diffuse lesions, both types show a predilection for the knee joint, a slight predisposition in female patients, median age around 47 years at first treatment, and are primarily treated with an open resection. The recurrence rate

in the diffuse type is 2.6 times higher compared with the localized-extremity type. TGCT is still considered a rare disease, though is more common than previously understood.

## Supplementary data

An appendix is available as supplementary data in the online version of this article, http://dx.doi.org/ 10.1080/ 17453674. 2017.1361126

## Acknowledgements

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# 2

# 3

# Tenosynovial Giant Cell Tumors in Children: A Similar Entity Compared With Adults

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Clinical Orthopaedics and Related Research. 2018 Feb 8 [Epub ahead of print].

# Abstract

Tenosynovial giant cell tumor (TGCT) is a rare, benign, mono-articular entity. Many case series in adults are described, whereas TGCT is only incidentally reported in children. Therefore, its incidence rate and natural history in children are unknown.

## Questions/ purposes

(1) How many cases have been reported of this condition, and what were their characteristics?
(2) What is the standardized pediatric incidence rate for TGCT?
(3) Is there a clinical difference in TGCT between children and adults?
(4) What is the risk of recurrence after open resection in children compared with adults?

## Data were derived from three sources:

(1) a systematic review on TGCT in children, seeking sources published between 1990 and 2016, included 17 heterogeneous, small case-series;
(2) the nationwide TGCT incidence study: the Dutch pediatric incidence rate was extracted from this nationwide study by including patients younger than 18 years of age. This registry-based study, in which eligible patients with TGCT were clinically verified, calculated Dutch incidence rates for localized and diffuse-type TGCT in a 5-year timeframe. Standardized pediatric incidence rates were obtained by using the direct method;
(3) from our nationwide bone and soft tissue tumor data registry, a clinical data set was derived. Fifty-seven children with histologically proven TGCT of large joints, diagnosed and treated between 1995 and 2015, in all four tertiary sarcoma centers in The Netherlands, were included. These clinically collected data were compared with a retrospective database of 423 adults with TGCT. Chi-square test and independent t-test were used to compare children and adults for TGCT type, sex, localization, symptoms before diagnosis, first treatment, recurrent disease, follow-up status, duration of symptoms, and time to follow-up. The Kaplan-Meier method was used to evaluate recurrence-free survival at 2.5 years.

TGCT is seldom reported because only 76 pediatric patients (39 female), 29 localized, 38 diffuse, and nine unknown type, were identified from our systematic review. The standardized pediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years in localized and diffuse types, respectively. From our clinical data set, symptoms both in children and adults were swelling, pain, and limited ROM with a median time before diagnosis of 12 months (range, 1-72 months).

With the numbers available, we did not observe differences in presentation between children and adults in terms of sex, symptoms before diagnosis, first treatment, recurrent disease, follow-up status, or median time to follow-up. The 2.5-year recurrence-free TGCT survival rate after open resection was not different with the numbers available between children and adults: 85% (95% confidence interval [CI], 67%-100%) versus 89% (95% CI, 83%-96%) in localized, respectively (p = 0.527) and 53% (95% CI, 35%-79%) versus 56% (95% CI, 49%-64%) in diffuse type, respectively (p = 0.691).



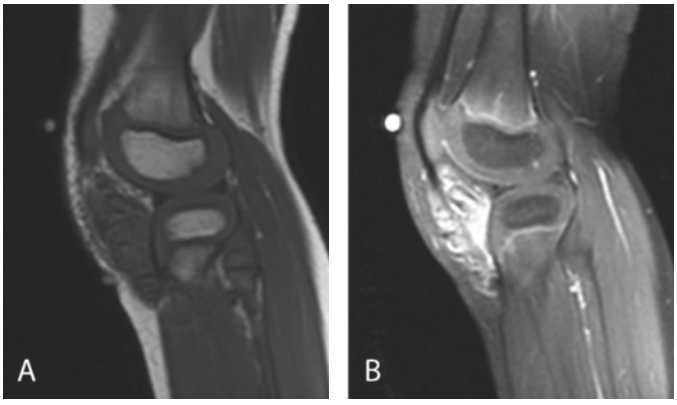
Although the incidence of pediatric TGCT is low, it should be considered in the differential diagnosis in children with chronic mono-articular joint effusions. Recurrent disease after surgical treatment of this orphan disease seems comparable between children and adults. With targeted therapies being developed, future research should define the most effective treatment strategies for this heterogeneous disease.

# Introduction

Tenosynovial giant cell tumor (TGCT) is a benign, mono-articular entity. Two histologically identical but clinically different types are distinguished: localized and diffuse lesions.[1] This distinction can be made either on MRI or at the time of surgery. The localized type is defined by the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone of 2013[87] as a well-circumscribed benign small lesion (figure. 1). By contrast, the diffuse type, previously named pigmented villonodular synovitis (PVNS), shows unclear boundaries with extensive involvement of the entire synovial membrane and infiltrative growth through adjacent structures (figure. 2).[1] The knee is the most common large joint affected by TGCT with 46% of localized and 64% of diffuse-type TGCTs affecting that joint; the hand and wrist are the next most common joints affected by the localized form, and the ankle and hip are the next most common joints affected by diffuse TGCT.[18] Delayed diagnosis is not uncommon as a result of different nonspecific clinical signs and symptoms,[37,88] and the definitive diagnosis must be made histologically. The standard treatment remains surgical resection, but recurrence occurs in 4% to 6% patients with localized and 14% to 40% diffuse TGCT affecting the knee[37]. Histologic or radiologic risk factors for recurrent disease are unknown.

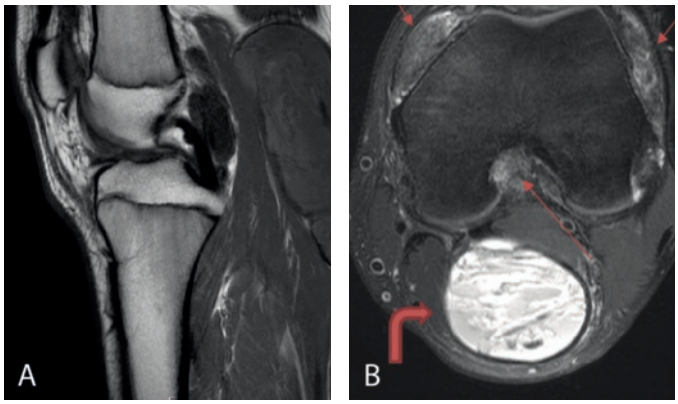
All described case-series on TGCT concern adults, whereas TGCT is only incidentally reported in children. Owing to the rarity of the disease, the available

**Figure 1A-B** Localized type TGCT.




MRI of a 6-year-old boy with TGCT in his left knee. (**A**) Sagittal T1-weighted image showing a well-circumscribed nodular lesion at the synovial lining of the anterior knee compartment. (**B**) Sagittal T1-weighted spectral presaturation with inversion recovery (SPIR) image after IV gadolinium administration shows hetero-geneous enhancement.

**Figure 2A-B** Diffuse type TGCT.




MRI of a 16-year-old boy with TGCT in his left knee. (**A**) Sagittal T1-weighted turbo spin echo (TSE) image shows extensive intra- and extra-articular villous proliferation of synovium. Posterior is a large Baker's cyst. (**B**) Transversal T2-weighted TSE image with heterogeneous low to intermediate signal of the TGCT anterior and posterior (straight arrow). Baker's cyst is shown posteriorly (curved arrow).

evidence base on TGCT contains predominantly retrospective, relatively small cohort studies, including heterogeneous data.[75] Sufficient data on pediatric patients with TGCT are lacking.

We therefore combined a systematic review with analysis from a nationwide pediatric TGCT incidence study in The Netherlands[18] and clinical data on TGCT in children and adults from four tertiary sarcoma centers in The Netherlands to answer the following questions: (1) How many cases have been reported of this condition, and what were their characteristics? (2) What is the standardized pediatric incidence rate for TGCT? (3) Is there a clinical difference in TGCT between children and adults? (4) What is the risk of recurrence after open resection in children compared with adults?

## Patients and Methods

Children were defined as patients younger than 18 years at presentation. Large joints were defined as all joints proximal to the metatarsophalangeal and metacarpophalangeal joints.

Data were derived from three sources: a systematic review, the nationwide TGCT incidence study, and from our bone and soft tissue tumor data registry.
A systematic review on TGCT in children was performed, seeking sources published

**Table 1** Literature overview on TGCT affecting all joints in children, including at least two TGCT cases (1990-2016, English language)*

| Study | Year | Number | Sex | Mean age (years; range) | Symptoms before diagnosis | Mean duration of symptoms (months; range) |
|---|---|---|---|---|---|---|
| Givon et al.[90] | 1991 | 2 | 1 M, 1 F | 7 (7-7) | S, W, LROM | 60 (both patients) |
| Rosenberg et al.†[91] | 2001 | 2 | 2 M | 12 (10-14) | S | NA |
| Neubauer et al.‖ [92] | 2007 | 5 | 3 M, 2 F | 12 (8-15) | S,P | 10 (2-24) |
| Gholve et al.‖ [89] | 2007 | 11 | 6 M, 5 F | 12 (7-16) | S, P | 10 (1-24) |
| Pannier et al.† [93] | 2008 | 6 | 2 M, 4 F | 12‡ | NA | NA |
| Baroni et al.[88] | 2010 | 9 | 4 M, 5 F | 11 (7-15)¶ | S, P, LROM | 18 (2-48) |
| Current | 2017 | 57 | 24 M, 33 F | 14 (4-18) | S, P, LROM | 16 (1-72) |
| Also adult cases included | | | | | | |
| Abdul-Karim et al.[94] | 1992 | 2 | 2 M | 10 (10-10) | S, P | NA |
| de Visser et al.[19] | 1999 | 5 | 4 M, 1 F | 16 (12-18) | NA | NA |
| Perka et al.[95] | 2000 | 2 | 2 F | 12 (8-16) | S, P, LROM | 12‡ |
| Somerhausen and Fletcher[96] | 2000 | 4 | 3 M, 1 F | 14 (3-18) | S | 7 (6-8) |
| Gibbons et al.[97] | 2002 | 3 | 1 M, 2 F | 11 (8-15) | S | 28 (6-96)§ |
| Bisbinas et al.[98] | 2004 | 5 | 5 F | 14 (12-15) | S | 2‡ |
| Brien et al.[99] | 2004 | 3 | 1 M, 2 F | 13 (12-15) | S, P | 7 (1-24)§ |
| Sharma et al.[100] | 2006 | 4 | 2 M, 2 F | 14 (8-17) | S, P | 2‡ |
| Sharma et al.[101] | 2007 | 3 | 2 M, 1 F | 17 (16-18) | S, P | 5 (2-9) |
| Nakahara et al.[102] | 2012 | 3 | 2 M, 1 F | 11 (8-13) | NA | NA |
| van der Heijden et al.[20] | 2014 | 7 | 2 M, 5 F | 14 (6-18) | NA | NA |
| Total | | 133 | | | | |

* Large joints were defined as all joints proximal to and excluding metatarsophalangeal and metacarpophalangeal joints; large case-series not describing children in detail were not included.
† Language of article was French; included information is based on an English abstract.
‡ Range unavailable.
§ Including adult cases.
‖ TGCT cases in digits were excluded.
{ Case number 6, a 2-year-old girl, was excluded according to a delayed time to diagnosis of 38 months.

TGCT = tenosynovial giant cell tumor; M = male; F = female; NA = information not available; S = swelling; W = warmth; LROM = limited ROM; P = pain; L = localized TGCT; D = diffuse TGCT; AS = arthroscopic synovectomy; OS = open synovectomy; US = unspecified synovectomy; MT = medical treatment; WS = wait-and-see treatment; AP = belowknee amputation; RS = radiosynovectomy.

| TGCT type | Joint | Primary surgeries | Recurrent disease | Mean follow-up (months; range) |
|---|---|---|---|---|
| 1 L, 1 D | 2 knee | 1 AS, 1 US | 0 | 24 (12-36) |
| 1 L, 1 D | 2 knee | 1 OS, 1 US | NA | NA |
| 5 unknown | 4 knee, 1 ankle | 5 AS | 1 | 36 (12-84) |
| 11 L | 2 knee, 3 ankle, 4 foot, 1 hand, 1 wrist | 11 OS | 0 | 54 (15-130) |
| 2 L, 4 D | 5 knee, 1 ankle | 5 US, 1 MT | 2 | 58‡ |
| 4 L, 5 D | 9 knee | 4 AS, 5 OS | 0 | 82 (46-143) |
| 28 L, 29 D | 32 knee, 11 ankle, 5 foot, 4 hip, 2 hand, 2 other, 1 wrist | 9 AS, 47 OS, 1 WS | 23 | 55 (0-260) |
| 2 D | 1 foot, 1 ankle | 1 US, 1 AP | 0 | 132 (108-156) |
| 5 D | 4 knee, 1 ankle | 4 US, 1 RS | 5 residual disease | 30 (21-75) |
| 2 L | 2 knee | 2 US | 0 | NA |
| 4 D | 1 knee, 1 foot, 1 buttock, 1 thigh | 4 US | 0/1 NA | 44.5 (0-114) |
| 3 L | 3 foot | 3 US | 0 | NA |
| 5 L | 5 ankle | 5 OS | 0 | 46 (12-150) |
| 3 D | 2 foot, 1 ankle | 3 US | 2 | NA |
| 4 unknown | 4 ankle | 4 US | 0 | 37.5 (19-65) |
| 3 D | 3 knee | 3 OS | 1 | 96 (54-138) |
| 3 D | 3 knee | 3 OS | 0 | 29 (20-36) |
| 7 D | 7 knee | 4 AS, 3 OS | 4 | 95 (24-212) |
| 57 L, 67 D, 9 unknown | | | | |

between 1990 and 2016. Search terms and MeSH headings were "tenosynovial giant cell", "diffuse type giant cell", "giant cell tumors", "PVNS", "pigmented villonodular synovitis", and "synovitis, pigmented villonodular" combined with "infant", "child", "neonat", "pediatric", "paediatric", "toddler", "teen", "teenager", "juvenile", "adolescent", "girl", and "boy". A total of 619 articles were identified in PubMed, EMBASE, and Cochrane library. All titles and abstracts were screened by two independent reviewers (MJLM, DU) including case series with at least two TGCT pediatric patients and published in English. Case series without detailed data on children were excluded, resulting in a data set of 17 heterogeneous, mostly small case series of two to six patients (Table 1). The largest study included 11 patients with localized TGCT of large joints[89].

The Dutch pediatric incidence rate was extracted from the nationwide TGCT incidence study by including patients < 18 years of age.[18] Standardized incidence rates were obtained by using the direct method, applying age-specific incidence rates in each 1-year age group to the WHO standard population (http://seer.cancer.gov). This study by Mastboom et al.[18] was a registry-based study and eligible patients with TGCT were clinically verified.

Patients without histologically proven TGCT were not included.

From our national bone and soft tissue tumor data registry (PALGA), a clinical data set was derived, including 57 patients < 18 years with (histologically proven) TGCT in large joints, treated between 1995 and 2015, in one of the four tertiary sarcoma centers in The Netherlands. Clinical, biologic, and imaging data on TGCT type, sex, localization, age at diagnosis, symptoms before diagnosis, treatment(s), recurrence(s), and follow-up were collected.

A combined retrospective database of two tertiary oncology centers (Leiden University Medical Center and Radboud University Medical Center) in The Netherlands has recorded all patients with TGCT since 1990 (455 patients). TGCT data on children were compared with TGCT data on 423 adults (32 children within this database were excluded from the adult group).

Statistical analyses, for our clinical data set, were pre-dominantly descriptive. Chi-square test was used to compare children and adults on TGCT type, sex (male versus female), localization (knee versus other large joints [hip, ankle, and foot]), symptoms before diagnosis (pain, swelling, and loss of function: yes versus no), first treatment (arthroscopic resection versus open resection), recurrent disease (no recurrence versus recurrence), and follow-up status. Independent t-test was used to compare median duration of symptoms and median time to follow-up. All reported p values were two-tailed. Statistical significance level was defined at $p < 0.05$. The recurrence-free survival curve was assessed with Kaplan-Meier methods.

This study was approved by the institutional review board from the Leiden University Medical Center (medical ethical approved protocol P13.029). Data capturing

and analyses were performed at Leiden University Medical Center. SPSS Version 23 (Chicago, IL, USA) was used for analyses.

## Results

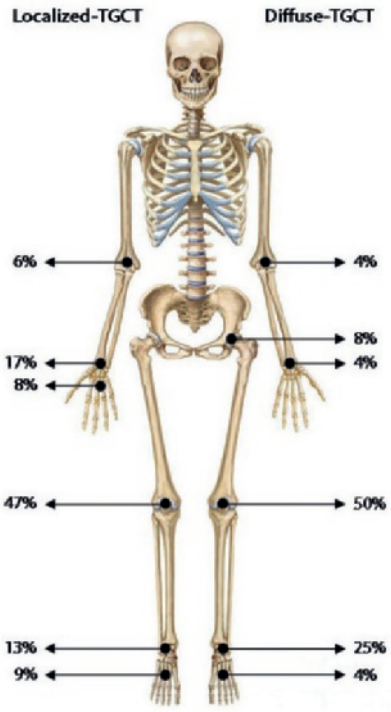


Our systematic review identified 17 case series involving 76 children (39 female) with TGCT, 29 localized, 38 diffuse, and nine unknown type (table 1). The pediatric group ranged from 3 to 18 years of age. The knee was most frequently affected (44 [58%]). Swelling, pain, and limited ROM were described symptoms before diagnosis (mean duration, 15 months). The majority of patients were primarily treated with synovectomy, either arthroscopic or open. Recurrent disease was described in 10 patients (13%). Only five pediatric studies described function or quality of life after treatment. Patients with (multiple) recurrences experienced impaired function and quality of life, according to van der Heijden et al.[20] Five children with diffuse TGCT, described by de Visser et al.[19], had fair to excellent results on the Musculoskeletal Tumor Society (MSTS) score after surgical treatment (MSTS by Enneking). Gholve et al.[89] described 11 children with surgically treated localized TGCT without disabling joint function according to a telephone questionnaire survey. Seven surgically treated children, described by Baroni et al.[88], recovered full ROM and two patients showed impaired joint movement with occasional mild to moderate pain in four children with localized and five children with diffuse type. Nakahara et al.[102] showed three children with diffuse disease of the knee with almost maximum Knee Society Scores and improved post-operative ROM of at least 0° to 145°.

The standardized pediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years in localized and diffuse types, respectively[18]. Between 2009 and 2013, 53 children with localized TGCT (excluding digits) and 24 children with diffuse TGCT were diagnosed in The Netherlands. This resulted in a Dutch incidence rate of 2.86 per million person-years for localized TGCT (excluding digits) and 1.30 per million person-years for diffuse TGCT; this was converted to standardized incidence rates (table, supplemental digital content 1). In both localized and diffuse types, the knee was most commonly affected (figure 3).

Clinical data of TGCT in children from the four Dutch tertiary sarcoma centers seemed similar to those observed in the combined two Dutch retrospective adult databases (table 2). Fifty-seven children (median age at diagnosis, 16 years; range, 4-18 years) with TGCT of large joints were identified (table 2). Symptoms before diagnosis were swelling, pain, and limited ROM with a median duration of 12 months (range, 1-72 months). These symptoms and the diagnostic delay seemed similar to those observed in adults (table 2). Children showed a localized diffuse

**Figure 3** Skeleton showing TGCT localization in children extracted from a Dutch incidence study, excluding digits.[103]




In diffuse TGCT, one patient was classified as "other"; he was treated for TGCT in his vertebral column.

ratio of one to one; the knee was predominantly affected (13 of 28 [46%] localized, 19 of 29 [66%] diffuse) and there was a predilection for females (15 of 28 [54%] localized, 18 of 29 [62%] diffuse). In 423 adults, the localized: diffuse ratio was 1:1.6; the knee was predominantly affected (121 of 172 [70%] localized, 189 of 251 [75%] diffuse) with a predilection for females (107 of 172 [62%] localized, 142 of 251 [57%] diffuse).

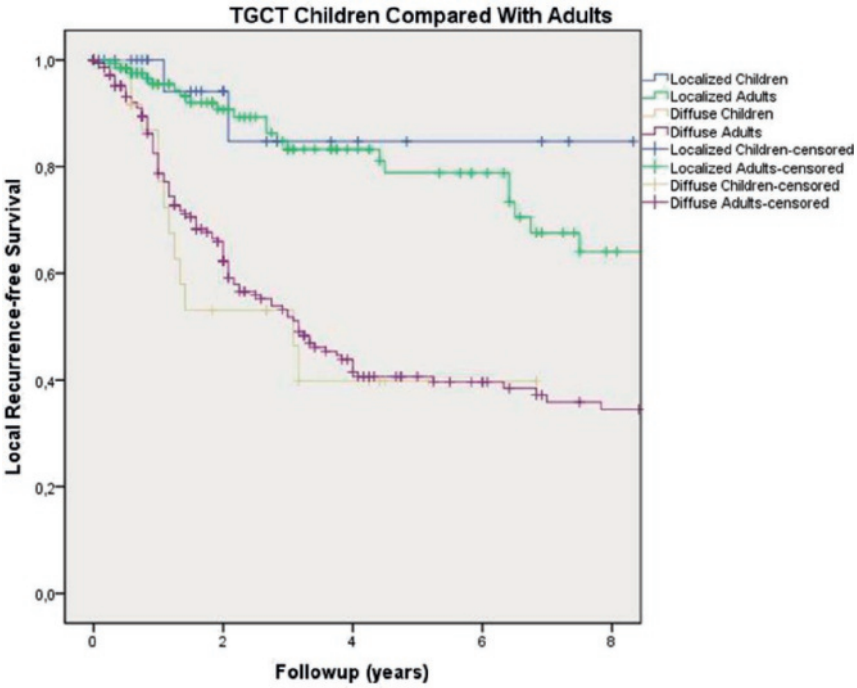
Recurrence-free survival curves were not different with the numbers available between children and adults at the four involved tumor centers (figure 4). The 2.5-year recurrence-free survival, after surgical treatment, in pediatric patients compared with adults was 85% (95% confidence interval [CI], 67%-100%) versus 89% (95% CI, 83%-96%; p = 0.527) in localized and 53% (95% CI, 35%-79%) versus 56% (95% CI, 49%-64%; p = 0.691) in diffuse type, respectively. In the four involved sarcoma centers, most children and adults alike were primarily surgically treated by open

**Table 2** Details of patients with TGCT of large joints in children versus adults, including sex, localization, age, symptoms, first treatment, recurrent disease, and follow-up†

| Patient variables | Children | | Adults | | Children versus adults | |
|---|---|---|---|---|---|---|
| | Localized TGCT | Diffuse TGCT | Localized TGCT | Diffuse TGCT | p value for localized TGCT | p value for diffuse TGCT |
| Total number of patients | 28 | 29 | 172 | 251 | | |
| **Sex** | | | | | 0.285 | 0.434 |
| Male:female ratio | 13:15(1:1.2) | 11:18(1:1.6) | 65:107(1:1.6) | 109:142 (1:1.3) | | |
| **Localization** | | | | | 0.019 | 0.207 |
| Knee | 13 (46%) | 19 (66%) | 121 (70%) | 189 (75%) | | |
| Other joints | 15 (54%) | 10 (34%) | 51 (30%) | 62 (25%) | | |
| **Age** | | | | | | |
| Median age at diagnosis (years; range) | 16 (4-18) | 16 (11-18) | 42 (19-82) | 38 (19-72) | | |
| **Symptoms before diagnosis** | | | | | | |
| Swelling | 24 (86%) | 21 (72%) | 106 (62%) | 163 (65%) | 0.010 | 0.510 |
| Pain | 12 (43%) | 17 (59%) | 103 (60%) | 157 (63%) | 0.129 | 0.558 |
| Limited ROM | 3 (11%) | 4 (14%) | 13 (8%) | 49 (20%) | 0.608 | 0.486 |
| Median duration of symptoms (months; range) | 9 (1-48) | 18 (1-72) | 12 (1-240) | 24 (1-300) | 0.176 | 0.153 |
| **First treatment** | | | | | 0.486+ | 0.289+ |
| Arthroscopic resection | 3 (11%) | 6 (21%) | 7 (4%) | 37 (15%) | | |
| Open resection | 25 (89%) | 22 (76%) | 147 (85%) | 188 (75%) | | |
| Wait and see Recurrent disease† | 0 | 1 (3%) | 18 (11%) | 26 (10%) | | |
| | N = 28 | N = 28 | N = 154 | N = 225 | 0.280 | 0.407 |
| No recurrence | 26 (93%) | 17 (61%) | 132 (86%) | 106 (47%) | | |
| $ 1 recurrence | 2 (7%) | 11 (39%) | 22 (14%) | 119 (53%) | | |
| **Follow-up status** | | | | | 0.840 | 0.768 |
| Disease-free | 19 (68%) | 16 (55%) | 110 (64%) | 121 (48%) | | |
| Alive with disease‡ | 4 (14%) | 9 (31%) | 19 (11%) | 94 (37%) | | |
| Death of other disease | 0 | 0 | 0 | 2 (1%) | | |
| Lost to follow-up‡ | 5 (18%) | 4 (14%) | 43 (25%) | 34 (14%) | | |
| Median time to follow-up (months; range)* | 25 (7-100) | 77 (7-144) | 36 (6-301) | 54 (6-350) | 0.127 | 0.780 |

*Patients lost to follow-up are excluded for median time to follow-up; lost to follow-up is defined as < 6 months follow-up; †+wait and see treatment was not included in calculation of independent t-test; children were included between 1995 and 2015 adults between 1990 and 2015; ‡patients alive with disease either have wait and see treatment, residual or recurrent disease; TGCT = tenosynovial giant cell tumor.

**Figure 4** Local recurrence-free survival curve of localized and diffuse TGCT (Kaplan-Meier), excluding digits.




Time zero is the time of the primary surgery. All patients were surgically treated; patients treated with wait-and-see treatment are excluded. In the adult graph, two patients died and were censored at the time of death if recurrence had not occurred.

resection: localized TGCT in 25 of 28 children (89%) were thus treated compared with 142 of 172 adults (85%; p = 0.486); for diffuse TGCT in children, the proportion was 22 of 29 (76%) compared with 188 of 251 in adults (75%; p = 0.289). Recurrence risk in children and adults was likewise not different with the numbers available: two of 28 (7%) compared with 22 of 172 (13%; p = 0.365) in localized type and 11 of 29 (38%) compared with 119 of 251 (47%; p = 0.921) in diffuse type, respectively.

## Discussion

TGCT is most commonly seen in adults in the third and fourth decades of life, but this study confirms that it also affects pediatric patients. The pediatric incidence rate for both localized and diffuse types suggests that it is rare, but we believe it is still common enough to include in the differential diagnosis of both children and adults with nonspecific symptoms like swelling, pain, and limited ROM. We found no differences with the numbers available between children and adults in terms of presenting symptoms, treatments used in the few available case series, and recurrence-free survival rates. In the era of personalized medicine, future research should define the most effective treatment for TGCT, with its various clinical scenarios, both in children and adults.



There are some limitations to this study. In our systematic review, many case series included data from children with TGCT in embedded studies that also contained adults' data. When data on children were not separately described, these children were not included in the overview (Table 1). The determined incidence rate is a conservative estimate, because our search was based on the nationwide network and registry of histo- and cytopathology in The Netherlands.[85] Patients with TGCT without a biopsy or treatment were not represented in this pathology-based cohort. By standardizing incidence rates, they could be extra-polated to other populations. However, generalizability of the standardized incidence rate depends on the age-specific population structure of the country compared with the WHO population. Included patients had histologically proven TGCT by a dedicated musculoskeletal pathologist (UF, HB, AS, JB). However, patients were not centrally reviewed for this study. Neither functional outcome nor quality of life was evaluated. For TGCT treatment, only surgical treatment was evaluated. Future, comparative studies on treatments should determine what should be done for patients (children and adults) with TGCT. Although surgery is the mainstay, other treatments are used, and future research needs to define what the best approaches are for the various clinical scenarios in which this disease presents. In our patients, children with the localized type frequently lacked longer term follow-up, mainly as a result of absence of clinical symptoms (17 censored in the first 2.5 years; figure 4). Smaller patient numbers with the diffuse type sometimes lacked longer follow-up (nine censored in the first 2.5 years).

TGCT does not seem to be an adults-only disease and should be considered in the differential diagnosis in children with (chronic) mono-articular joint effusion. Our systematic review identified mainly small, heterogeneous TGCT case series in children. Future studies might consider including children with TGCT to allow for optimization of the treatment protocol in both children and adults.

The standardized pediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years compared with an overall incidence rate of 10.2 and 4.1 per million person-years in localized and diffuse types, respectively.[18] To date, the incidence rate for chronic mono-arthritis in children and adolescents is unknown. Savolainen et al.[104] calculated an incidence rate of 64 per 100,000 for all types of arthritis in children (< 16 years) in a defined population in Finland. Although TGCT in children probably accounts for only a small percentage of all types of arthritis, it should still be considered in the differential diagnosis.
Symptoms in children seemed similar to those in adults (Table 1). Nonspecific symptoms accompanied by pain and diffuse joint swelling with thickening of the synovial capsule and/or joint effusion resulted in limited movement in approximately half of the patients. Studies in adults add mechanical symptoms, instability, and stiffness.[37,105]

A systematic review (without age limitations) in 2013[37] reported average recurrence rates for localized TGCT in the knee after open resection (4%) and after arthroscopic resection (6%) in contrast to the diffuse type after open resection (14%) and after arthroscopic resection (40%) at a mean follow-up of 108 months. Patel et al.[105] presented 214 patients with knee TGCT of all ages with a recurrence rate of 9% in 100 localized patients and 48% in 114 patients with diffuse TGCT after a mean follow-up of 25 months (range, 1-168 months). Palmerini et al.[38] reported 294 patients with TGCT of all ages in all joints with a local failure rate of 14% in localized and 36% in diffuse type after a median follow-up of 4.4 years (range, 1-20 years). The sole primary disease or patients with a first relapse were included. The current pediatric case-series showed comparable recurrence rates of 7% in localized and 39% in diffuse type after a mean follow-up of 55 months (range, 7- 350 months).

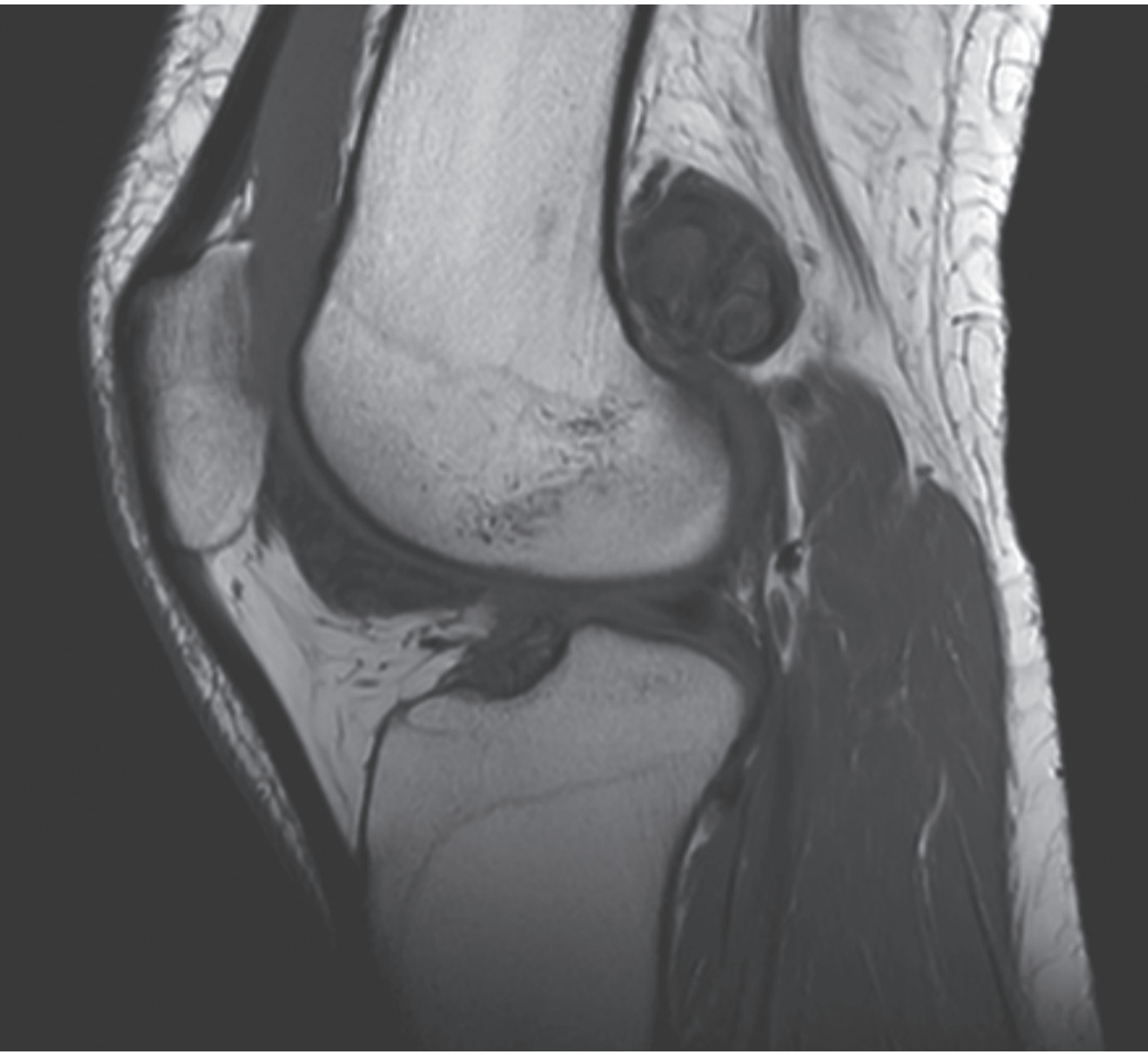
TGCT is a rare condition in adults and it is even less common in children. Nonspecific symptoms often contribute to a delay in establishing a diagnosis. TGCT should be considered in chronic mono-arthritis both in adults and in children. Recurrent disease after surgical treatment of this orphan disease seems comparable between children and adults. With targeted therapies now being developed[16], future research should define the most effective treatment strategies for this heterogeneous disease.

## Acknowledgments

We thank the dedicated musculoskeletal pathologists, Uta Flucke, Hans Bras, Albert Suurmeijer, and Judith Bovee, for their contributions in diagnosing TGCT.

# 3

# Diagnosis



# 4

# Severity Classification of Tenosynovial Giant Cell Tumours on MR Imaging

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## Abstract

Current development of novel systemic agents requires identification and monitoring of extensive Tenosynovial Giant Cell Tumours (TGCT). This study defines TGCT extension on MR imaging to classify severity.

In part one, six MR parameters were defined by field-experts to assess disease extension on MR images: type of TGCT, articular involvement, cartilage-covered bone invasion, and involvement of muscular/tendinous tissue, ligaments or neurovascular structures. Inter- and intra-rater agreement were calculated using 118 TGCT MR scans. In part two, the previously defined MR parameters were evaluated in 174 consecutive, not previously used, MR-scans. TGCT severity classification was established based on highest to lowest Hazard Ratios (HR) on first recurrence.

In part one, all MR parameters showed good inter- and intra-rater agreement (Kappa≥0.66). In part two, cartilage-covered bone invasion and neurovascular involvement were rarely appreciated (<13%) and therefore excluded for additional analyses. Univariate analyses for recurrent disease yielded positive associations for type of TGCT HR12.84(95%CI4.60–35.81), articular involvement HR6.00(95%CI2.14–16.80), muscular/tendinous tissue involvement HR3.50(95%CI1.75–7.01) and ligament-involvement HR4.59(95%CI2.23–9.46). With these, a TGCT severity classification was constructed with four distinct severity-stages. Recurrence free survival at 4 years (log rank p<0.0001) was 94% in mild localized (n56, 1 recurrence), 88% in severe localized (n31, 3 recurrences), 59% in moderate diffuse (n32, 12 recurrences) and 36% in severe diffuse (n55, 33 recurrences).

The proposed TGCT severity classification informs physicians and patients on disease extent and risk for recurrence after surgical treatment. Definition of the most severe subgroup attributes to a universal identification of eligible patients for systemic therapy or trials for novel agents.

# Introduction

Tenosynovial Giant Cell Tumour (TGCT) affecting large joints is an orphan, monoarticular, potentially locally aggressive disease with high recurrence rates. According to the 2013 WHO classification of tumours of soft tissue and bone, at the base of growth pattern, a radiological distinction is made between single nodule (localized-TGCT) and multiple lesions (diffuse-TGCT). These types differ in their clinical presentation, response to treatment and prognosis, but histologically, they seem identical.[1,106]

Localized-type TGCT is classified as a circumscribed benign small (between 0.5 and 4 cm) mass.[1,18] Standard treatment of choice is excision. Subsequently, overall reported recurrence rates are relatively low: 0–6%.[37] On the contrary, diffuse-type TGCT, previously named Pigmented Villonodular Synovitis (PVNS), extensively involves the synovial membrane and infiltrates adjacent structures.[37,107] Reported recurrence rates of diffuse-TGCT following open synovectomy are 14% up till 67% and after arthroscopic synovectomy 40% up till 92%.[37] Recurrent or residual disease, frequently requiring multiple, sometimes mutilating operations, may result in total joint arthroplasties, morbidity and loss of quality of life.[20,42,43,80,108] With this large variety in disease presentation and recurrence rates, a more omprehensive and out- come-based classification is asked for. The emerging era of systemic targeted and multimodality therapies (available in trial settings) increases the need for a method to select eligible patients in order to create com- parable patient cohorts.[61,62,65]

In diagnosing and treating TGCT, magnetic resonance (MR) imaging is the most distinctive imaging technique.[30-32,60,109] MR imaging reveals conspicuous nodular (localized-type) or villous proliferation of synovium (diffuse-type). However, current literature lacks specific MR discriminating features to describe or quantify tumour extent in relation to clinical outcome. Uniform MR descriptions are of utmost importance for clinical and research purposes. Therefore this study aims to sub-classify tumour severity especially in diffuse-type TGCT. First, a group of radiologists and orthopaedic surgeons identified and defined potentially distinguishing parameters. Second, these MR parameters were applied on a different study-population to establish TGCT severity subgroups.

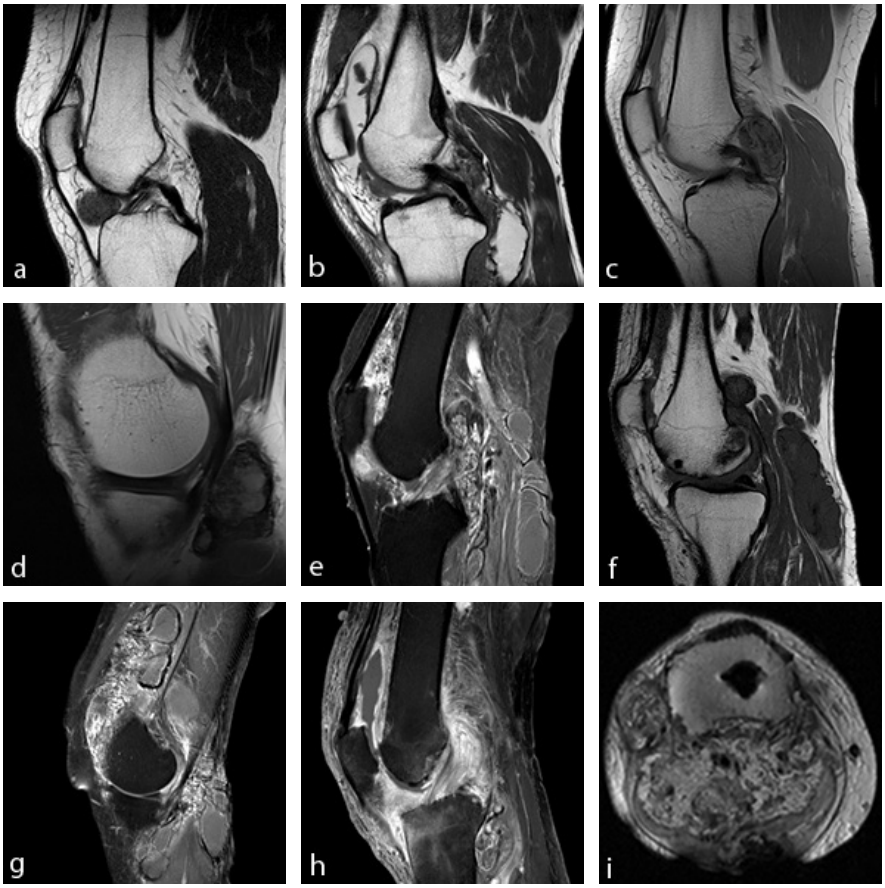
# Methods

### Part I: Identification and evaluation of TGCT specific MR parameters.

Using case discussions in expert meetings with two dedicated musculoskeletal radiologists and three oncological orthopaedic surgeons, six MR parameters were selected in relation to anatomical or surgical landmarks. These parameters were

1 type of TGCT (based on 2013 WHO classification[1]), 2 articular involvement, 3 cartilage-covered bone invasion, 4 involvement of muscular/tendinous tissue, 5 involvement of ligaments and 6 involvement of neurovascular structures (figure 1, appendix).

**Figure 1** Definition of six TGCT specific MR parameters




**TGCT-type**

**a**. Localized-type on a sagittal PD-weighted FSE MR image of a 49 year old female patient. Localized-TGCT is defined according to WHO as a well circumscribed nodular lesion at synovial lining of bursa, joint or tendon sheath.

b. Diffuse-type on a sagittal PD-weighted FSE MR image of a 24 year old male patient. Diffuse-TGCT is defined as a multinodular lesion involving a larger part or multiple compartments of the synovial lining.

**Articular involvement**

**c**. Intra-articular well circumscribed lesion on posterior cruciate ligament on a PD-weighted FSE MR image of a 18 year old female patient. Intra-articular involvement is defined as TGCT involvement inside synovial lining of joint.

**d**. Extra-articular involvement, along gastrocnemius muscle insertion, on a sagittal T1-weighted FSE MR image of a 33 year old male patient. Extra-articular involvement is defined as TGCT involvement outside synovial lining of the joint.

**e**. Both intra- and extra-articular involvement on a sagittal T1-weighted fat-suppressed MR image after intravenous administration of gadolinium of a 63 year old female patient with TGCT. Extensive tumour growth anterior and posterior.

**Cartilage-covered bone invasion**

**f**. Cartilage covered bone invasion on a sagittal T1-weighted FSE MR image of a 59 year old male patient. Square presents cartilage covered bone, defined as clear invasion of bone through cartilage; not only touch cartilage. Circle presents not-cartilage covered bone invasion.

**Muscular/tendinous tissue involvement**

**g**. Muscular/tendinous tissue involvement, anterior vastus medialis muscle and posterior hamstrings tendon, on a sagittal T1-weighted fat-suppressed MR image after intravenous administration of gadolinium of a 63 year old female patient with TGCT. Muscular/tendinous tissue is defined as involvement of muscular/tendinous tissue or >180 degrees encagement of tendon/muscle.

**Ligament involvement**

**h**. Cruciate ligament enhancement on a sagittal T1-weighted fat-suppressed MR image after intravenous administration of gadolinium of a 64 year old male patient. Ligament involvement is defined as involvement of ligament or >180 degrees encagement of ligament.

**Neurovascular structures involvement**

**i**. Popliteal artery encagement on an axial PD-weighted FSE MR image of a 62 year old female patient, referred to a tertiary sarcoma center with extensive TGCT. Neurovascular involvement is defined as > 180 degrees encagement of the artery or nerve.

FSE, Fast Spin Echo; PD, Proton Density

Figure e & g is the same female patient.



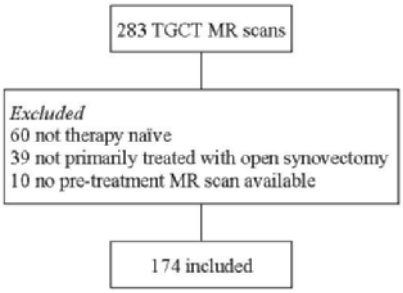
To evaluate usability and reproducibility, 118 MR scans of TGCT patients, treated at the Leiden University Medical Center (LUMC), were randomly retrieved (MM). The six MR parameters were evaluated in a heterogeneous group of TGCT cases as scans included cases of various large joints (knee (79; 67%), ankle (13; 11%), foot (10; 9%)), severity subtypes and treatment phases. MR scans were conducted using a 1.5 or 3.0 T unit Philips (Best, The Netherlands) Ingenia MR with dedicated coils. Standard musculoskeletal scan-protocol included: T1-and T2-weighted fast spin echo, T1-weighted fat-suppressed post Gd-chelate contrast and optionally $T2^*$ gradient-echo sequences in two planes (transversal and either sagittal or coronal). To assess inter- and intra-rater agreement, all MR scans were evaluated by one dedicated musculoskeletal radiologist (DH) and by two dedicated orthopaedic surgeons (RW, MS). MR evaluation was blinded to patient characteristics.

Inter-rater agreement and accompanying 95% confidence interval (95% CI) between three physicians was calculated for all 118 cases by Fleiss-Kappa (dichotomous outcomes in all parameters, except for articular involvement with three outcomes). To evaluate intra-rater agreement with the accompanying 95% CI (linear weighted kappa), 36 randomly chosen MR scans (31%) were again evaluated three months after initial evaluation by the senior orthopaedic surgeon (MS).

## Part II: Application of TGCT MR parameters.

None of the MR scans in part I were used in part II. The combined TGCT-database of two sarcoma centres in The Netherlands (LUMC and Radboud University Medical Center (RUMC)) was used to include consecutive MR scans conducted between 2005 and 2015 (n = 283). MR scan inclusion criteria were: pre-treatment MR scan of histologically proven TGCT of large joints, conducted in two planes (transversal and either sagittal or coronal), and open resection as primary treatment in one of the two participating centers. Large joints were defined as all joints proximal to and excluding metatarsophalangeal and metacarpophalangeal joints. When TGCT affected the knee, one diagnostic arthroscopy prior to open resection was allowed, since tumour extent would not be affected. Open synovectomy was defied as gross total resection of disease, either one- or two-staged, without adjuvant therapy. 174/283 Patients met the inclusion criteria (figure 2). Median follow-up was 36 (IQR 21–60) months, maximum follow-up 12 years after primary surgery.

**Figure 2** Inclusion flowchart part II TGCT severity classification.




The senior author (MS) evaluated the six defined MR parameters (part I) on these pre-treatment scans (77 LUMC, 97 RUMC). MR evaluation was blinded to patient characteristics and clinical outcome. Patient and tumour characteristics were gathered: gender, localization (affected joint), age at time of the MR scan, date of open synovectomy, first local recurrence and date of first recurrence (on MR imaging), and date of last follow-up. Median follow-up was calculated from date of primary surgery to date of last clinical follow-up, including interquartile range (IQR). Recurrence free survival was calculated from date of surgery to recurrent disease or last contact.

As outcome, first recurrence was defined as new disease presence after synovectomy or growing residual disease (diagnosed on follow-up MR scan). Proposed risk factors were gender, localization (knee versus other joints) and age at the time

of the MR scan (below or above 40 years). Hazard ratios (HRs) and their corresponding 95% CI were estimated for risk factors and MR parameters (part I) by univariate and multivariate Cox regression analyses to estimate the relation on recurrent disease. Since estimating HR is unreliable for rarely present MR parameters, only parameters with an adequate number of presence (minimum of 20%) were used for additional analyses. Recurrence free survival close to median time of follow-up was calculated by Kaplan Meier analyses and log rank test. Time zero was defined as date of primary open synovectomy.

At the base of HRs with positive associations of risk factors and MR parameters on first recurrences, the TGCT severity classification was established. The TGCT subgroup flow chart started with the MR parameter with highest HR, followed by descending HRs. Statistical Package for Social Statistics (SPSS) version 23 was used for analyses.



### Ethical statement

This study was approved by the institutional review board from our institution (registration number P13.029). No funding was received.

## Results

### Part I: Evaluation of TGCT specific MR parameters.

Inter-rater agreements for type of TGCT, articular involvement, cartilage-covered bone invasion, and involvement of muscular/tendinous tissue, ligaments or neurovascular structures were 0.71; 0.68; 0.66; 0.67; 0.75 and 0.73, respectively. Intra-rater agreements for these parameters were between 0.72 and 1.00 (table 1). Since inter- and intra-rater agreements were good [5] for these six MR features, all parameters were considered viable to use for TGCT subgroup analyses.

### Part II: Application of TGCT MR parameters.

Out of 174 MR scans, the knee was affected most (122; 70%), followed by the ankle (20; 12%) (table 2). In univariate analyses, none of the proposed risk factors were associated with recurrent disease ($p > 0.37$) (table 3) and consequently not used for further analyses. Both MR parameters cartilage-covered bone invasion and involvement of neurovascular structures were rarely seen on MR images (<13%) and in accordance with our exclusion criteria not used for additional analyses. In univariate analyses, the remaining four MR parameters were associated with recurrent disease ($p < 0.002$) (Table 3); strongest association was seen in diffuse-type compared with localized-type (HR 12.84(95%CI 4.60–35.81)), subsequently intra-and extra-articular involvement compared with extra-articular (HR 6.00 (95%CI 2.14–16.80))

and involvement of muscular/tendinous tissue or ligaments compared with no involvement (HR 3.50 (95%CI 1.75–7.01), HR 4.59 (95%CI 2.23–9.46), respectively).

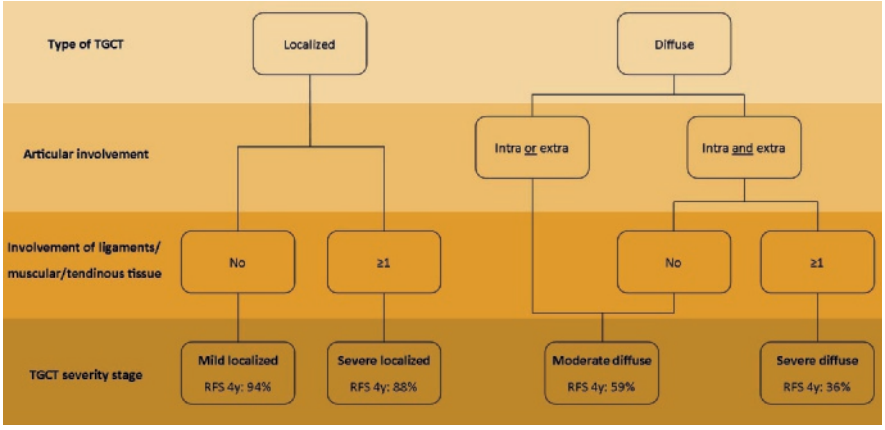
Multivariate analyses for MR parameters did not show individual positive association, except for parameter type of TGCT (supplementary material I).

Four TGCT severity subtypes were established using a flowchart that begins with the parameters with highest HR (parameter type of TGCT), followed by parameters with descending HRs. These four sub-types showed a clinically relevant or significant prognostic value for recurrent disease and were classified as: mild localized (n56, 1 recurrence), severe localized (n31, 3 recurrences), moderate diffuse (n32, 12 recurrences) and severe diffuse (n55, 33 recurrences).

1. Mild localized contained localized-type, either intra- or extra-articular involvement without involvement of muscular/tendinous tissue/ ligaments.
2. Severe localized included localized-type, either intra- or extra-articular lesions and either or both involvement of muscular/tendinous tissue/ligaments.
3. Moderate diffuse comprised diffuse-type with intra- and/or extra-articular disease without and involvement of muscular/tendinous tissue/ligaments.
4. Severe diffuse was diffuse-type including intra- and extra-articular involvement and involvement of at least one of the three structures (muscular/tendinous tissue/ligaments) (figure 3).

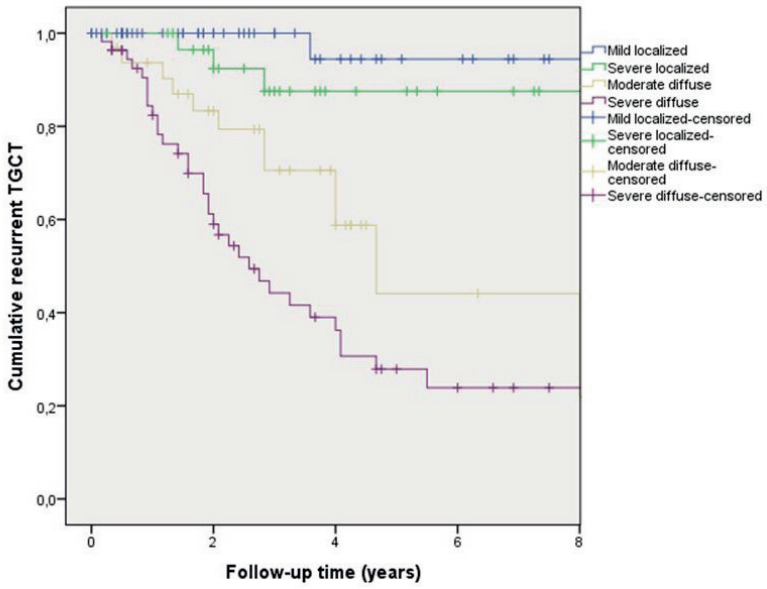
Recurrence free survival at 4 years (close to median follow-up diffuse-type) for the four patient groups according to the new MR sub-types descended from 94% in mild localized, to 88% in severe localized, to 59% in moderate diffuse and to 36%

**Figure 3** TGCT severity classification.




Four severity subtypes: mild localized, severe localized, moderate diffuse and severe diffuse. RFS 4y, recurrence free survival at 4 years.

**Figure 4** TGCT recurrence free survival curve for four TGCT severity subtypes, affecting large joints.




| Time (years) | 0 | 2 | 4 | 6 | 8 |
|---|---|---|---|---|---|
| Number at risk | 174 | 105 | 51 | 24 | 10 |

Time zero was date of primary open synovectomy. One patient, classified as severe diffuse died of another disease after 4 months and was censored at that time.

in the least favorable subtype, severe diffuse. Median time to local recurrence in moderate diffuse and severe diffuse subtypes was 29.5 (IQR 14.5–48.0) and 22.0 (IQR 11.8–33.5) months, respectively. Majority of recurrent disease cases were already treated with a re-operation (32/49, 65%). One patient, classified as severe diffuse, died of another disease, after four months and was censored at that time. Novel MR based TGCT severity and associated Kaplan Meier survival curves presented significant difference between the four patient groups (log rank p< 0.0001) and additional differentiation compared with solely sub-classifying in localized- and diffuse-TGCT (figure 4 and supplementary material II).

## Discussion

This is the first study to define severity subtypes in Tenosynovial Giant Cell Tumours (TGCT) based on a combination of four MR imaging parameters. These subtypes correlate with a spectrum of disease severity ranging from low to high risk of local recurrence after surgical intervention.

Within this present era of systemic targeted and multimodality therapies (available in trial settings) in TGCT, standalone surgical resection cannot be regarded the gold standard anymore for more severe cases.[70] Because of the lack of clear-cut boundaries in diffuse-TGCT, complete resection is difficult and at times technically impossible or undesirable with joint function preservation and quality of life in mind. In patients with locally advanced TGCT or (multiple) recurrence(s), systemic therapies targeting the CSF1/CSF1R axis have been investigated; less potent drugs as nilotinib and imatinib,[15,63] and more specific inhibitors as emactuzumab (RG7155), pexidartinib (PLX3397) and cabiralizumab (FPA008). Emactuzumab (N=29) had an overall response rate of 86% (two patients with a complete response) and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months).[15] In a randomized, placebo-controlled phase 3 study, pexidartinib showed an improved overall response rate by RECIST: 39% in the pexidartinib-group (N=61) and 0% of placebo-group (N=59), after median six months follow-up.[65] The preliminary results with cabiralizumab (N=22) are consistent, with radiographic response and improvement in pain and function in five out of 11 patients 28.[62] However, long term efficacy data have not yet been reported with these newer agents.

Patient inclusion for these trials is very heterogeneous. A strict patient selection is desirable, to accurately evaluate effect of these treatments. At present, patient selection for trial inclusion is established by preference of treating physician and might differ per center. Defining more aggressive TGCT subtypes and including these uniformly defined patients into trials would more adequately investigate the effect and toxicities of treatment.[71] In this study, we propose to include patients defined with 'severe diffuse' TGCT subtype. Monitoring the effect of systemic therapy would also benefit from clear agreements on parameters.

Uniform MR descriptions are of utmost importance for clinical and research purposes. Thus far, no well-defined tumour parameters exist. Definition of unambiguous MR criteria is challenging, because of the rarity of the tumour and small number of heterogeneous cases, variety of joints involved, different disease severity as well as several treatment modalities.[1,75] So far, MR imaging has shown to be the best discriminating method to evaluate TGCT.[30,110] In our study, six objective clinically relevant MR parameters were defined in relation to anatomical or surgical landmarks. According to our exclusion criteria for the development of

the severity classification, parameters cartilage covered bone invasion and neurovascular involvement showed inadequate number of presence and were therefore not used. However, in larger case series these two parameters might correlate with more aggressive disease and hence a higher recurrence rate.

To date, no radiology-based TGCT severity classification exists. Subdividing between localized- and diffuse-TGCT seems an oversimplification that fails to estimate differences in recurrent rates for individual patients. Murphey et al. presented an extensive review of different TGCT features on several imaging techniques, without relating these features to disease severity, treatment or recurrences.[30] Van der Heijden et al.[20] further sub-classified diffuse-TGCT affecting the knee in 30 patients into mild or severe, without linking to recurrent disease. Mild diffuse-TGCT was defined as involvement of either anterior or posterior compartment of the knee, with the cruciate ligaments as boundary. Severe diffuse-TGCT was defined as involvement of both compartments, with or without extra-articular extension.[20] In contrast to most literature, we selected a homogeneously treated patient population to develop four severity subtypes, by only including patients initially treated with an open synovectomy.



In line with most papers, especially papers on trial medication, and based on clinical practice, we included all large joints to sub-classify disease severity for TGCT. Prior research did not show a (significant) difference in recurrence rates for both localized and diffuse disease when comparing the knee with other joints.[37,38,75,111] A recent TGCT incidence calculation study showed a predominance of the knee in 46% in localized- and 64% in diffuse-type (excluding digits)[18], in line with our overrepresentation of the knee of 70%. In the future, a TGCT severity classification focused on the knee would contain more detailed knee-specific MR parameters and equal treatment approaches.

Limitations to this study: primary, the resulting HRs had wide confidence intervals, indicating low precision in the estimates. This is likely related to the relatively small sample size, given that the patients were divided into several groups based on the MR parameters. Secondly, because of the relatively small number of recurrences in severity subtypes mild localized (n 1) and severe localized (n 3), Hazard Ratios may be unreliable. Therefore, it was not feasible to estimate a cox model and to generate a true prediction model. Additionally, localized-TGCT is known to have few recurrences and often remains without clinical complaints after resection. In both sarcoma centers, patients are therefore discharged from follow-up after the first follow-up post-surgery and requested to return again when clinical complaints present. In our analyses, 31 localized-type patients were censored at date of last clinical follow-up within the first two years in survival curve (figure 4). Less often, patients with diffuse-type have also lacked follow-up (13 censored first two years). It could be assumed that these patients did not have

complaints and recurrent disease. Furthermore, in study part two (establishing TGCT subtypes), newest included MR scans originated from 2015. These cases had a maximum follow-up of two years. Since it is known that local recurrence might develop years after initial surgery[1,38,42], in our study a median of 29.5 in moderate diffuse and 22.0 months in severe diffuse-TGCT subtypes, underestimation of recurrence free survival could be present. Finally, even though quite a large number of MR scans (174) were used in development of the severity classification, in larger case-series including long follow-up time, it might be possible to differentiate further in disease severity and assess additional subtypes.

To conclude, in reporting TGCT affecting large joints on MR imaging, six parameters are helpful in discriminating disease extent. Patients can be accurately monitored by using these MR parameters. With respect to recurrence, a combination of four MR parameters classifies patients into one of four severity subtypes, presented with distinct recurrence free survival rates. In the era of personalized medicine, treatment is individualized for each patient depending on the extent of disease. Because histopathological prognostic factors are lacking, sub-classification of TGCT on MR imaging is a potential tool to stratify future patient prognosis and identify candidates for targeted therapies, thereby aiding with the decision in daily practice.

## Acknowledgement

The authors thank Lizz van der Heijden for reviewing the final draft of the manuscript.

# Tables and supplementary materials

**Table 1** Inter- and intra-rater agreement (kappa) in six MR parameters.

| Agreement | Type of TGCT | Articular involvement | Cartilage-covered bone invasion | Muscular/ tendinous tissue involvement | Ligament involvement | Neurovascular involvement |
|---|---|---|---|---|---|---|
| Inter-rater | 0.71 (0.60-0.81) | 0.68 (0.58-0.78) | 0.66 (0.56-0.76) | 0.67 (0.56-0.77) | 0.75 (0.57-0.93) | 0.73 (0.62-0.83) |
| Intra-rater | 0.94 (0.82-1.06) | 0.89 (0.74-1.04) | 0.79 (0.39-1.19) | 0.72 (0.50-0.94) | 0.86 (0.68-1.04) | 1.00 (1.00-1.00) |

Inter-rater, Agreement between three physicians from LUMC (one musculoskeletal radiologist, two orthopedic oncologists), calculated with Fleiss-Kappa.
Intra-rater, Agreement between senior orthopedic oncologist one, with 30% of MR scans re-evaluated 3 months after initial evaluation.
Interpretation of intra- and intra-rater agreement (K-value).[112]

**Agreement value strength of agreement**

| | |
|---|---|
| < 0.20 | Poor |
| 0.21 - 0.40 | Fair |
| 0.41 - 0.60 | Moderate |
| 0.61 - 0.80 | Good |
| 0.81 - 1.00 | Very good |

**Table 2** TGCT MR scan demographics.

| | Cases (%) | Cases localized-TGCT (%) | Cases diffuse-TGCT (%) |
|---|---|---|---|
| Total number of MR scans | 174 | 87 | 87 |
| Gender | | | |
| Female | 105 (60) | 33 (38) | 36 (41) |
| Male | 69 (40) | 54 (62) | 51 (59) |
| Median age at MR scan (IQR) | 37 (26-48) years | 37 (24-47) years | 36 (26-49) years |
| Localization | | | |
| Knee | 122 (70) | 63 (72) | 59 (68) |
| Hip | 8 (5) | 0 (0) | 8 (9) |
| Ankle | 20 (12) | 10 (11) | 10 (11) |
| Foot | 9 (5) | 5 (6) | 4 (5) |
| Elbow | 6 (3) | 4 (5) | 2 (2) |
| Other | 9 (5) | 5 (6) | 4 (5) |
| Median follow-up (IQR) | 36 (21-60) months | 32 (17-56) months | 41 (24-63) months |
| Total number of recurrences | | | |
| Recurrent disease | 49 (28) | 4 (5) | 45 (52) |
| No recurrent disease | 125 (72) | 83 (95) | 42 (48) |

IQR, interquartile range

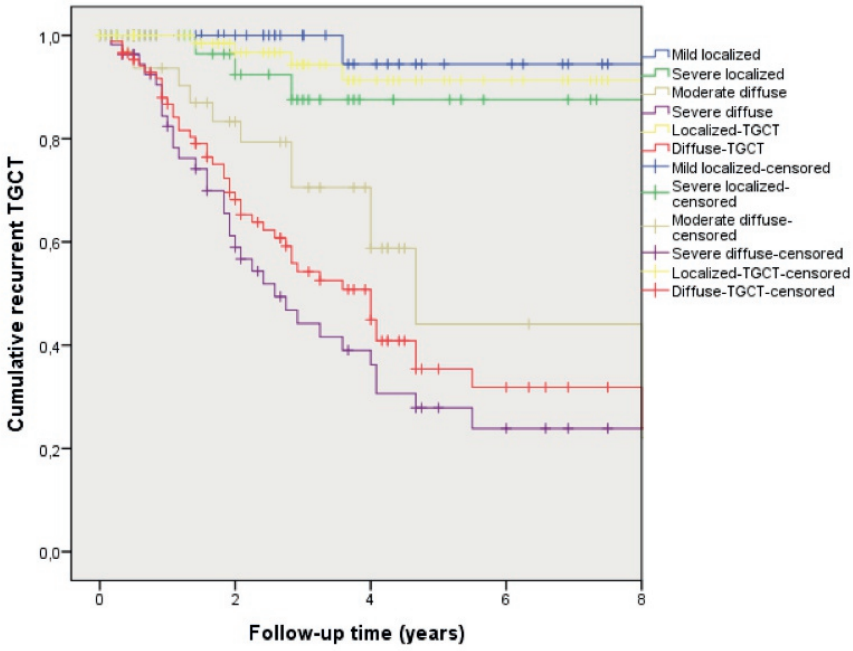
**Table 3** Risk of recurrence on MR imaging; univariate analyses in proposed risk factors and four MR parameters.

| | n (%) | Hazard ratio (95% CI) | P |
|---|---|---|---|
| Gender | | | |
| Male | 69 (40) | 1.29 (0.74-2.27) | 0.37 |
| Female | 105 (60) | 1 | |
| Age | | | |
| <40 years | 91 (52) | 1.15 (0.66-2.02) | 0.63 |
| >40 years | 83 (48) | 1 | |
| Localization | | | |
| Knee | 122 (70) | 1.15 (0.63-2.12) | 0.65 |
| Other joint | 52 (30) | 1 | |
| TGCT-type | | | |
| Diffuse | 87 (50) | 12.84 (4.60-35.81) | <0.000 |
| Localized | 87 (50) | 1 | |
| Articular involvement | | | |
| Intra-articular | 59 (34) | 1.11 (0.31-3.95) | 0.87 |
| Intra- and extra-articular | 75 (43) | 6.00 (2.14-16.80) | 0.001 |
| Extra-articular | 40 (23) | 1 | |
| Muscular/tendinous tissue involvement | | | |
| Yes | 90 (52) | 3.50 (1.75-7.01) | <0.000 |
| No | 84 (48) | 1 | |
| Ligament involvement | | | |
| Yes | 86 (49) | 4.59 (2.23-9.46) | <0.000 |
| No | 88 (51) | 1 | |

**Supplementary material I** Risk of recurrence on MR imaging, multivariate analyses.

| | Hazard ratio (95% CI) | P |
|---|---|---|
| TGCT-type | | |
| Diffuse | 7.79 (2.17-28.03) | 0.002 |
| Localized | 1 | |
| Articular involvement | | |
| Intra-articular | 1.86 (0.37-9.46) | 0.45 |
| Intra- and extra-articular | 1.20 (0.36-3.99) | 0.77 |
| Extra-articular | 1 | |
| Muscular/tendinous tissue involvement | | |
| Yes | 1.98 (0.70-5.58) | 0.20 |
| No | 1 | |
| Ligament involvement | | |
| Yes | 1.62 (0.71-3.69) | 0.26 |
| No | 1 | |

**Supplementary material II** TGCT recurrence free survival curve with four TGCT severity subtypes compared with solely sub-classifying by localized- or diffuse-TGCT, affecting large joints.




Time zero was date of primary open syno- vectomy. One patient, classified as severe diffuse died of another disease after 4 months and was censored at that time.

## Appendix TGCT MR parameters, affecting large joints, in therapy naïve primary TGCT patients

Agreement:
Involvement of a structure: when signal intensity is changed to TGCT signal intensity, this structure is considered to be involved with TGCT and to be scored.
When involvement of a structure is unclear: choose **'structure involved'** (when in doubt; over-scoring, not under-scoring).
MI parameters:
**TGCT-type**

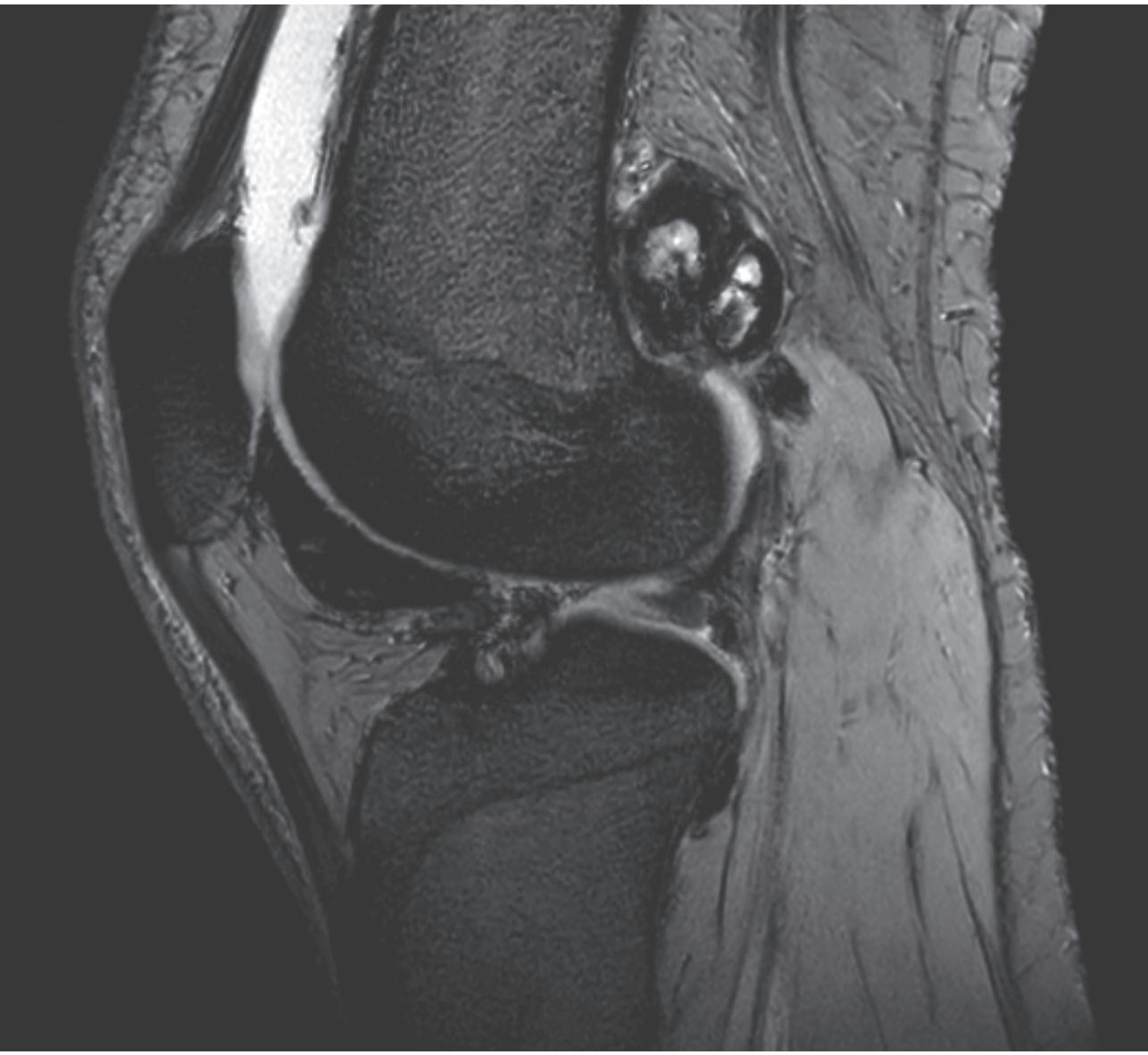
**Localized-type**[†]: well circumscribed nodular lesion at synovial lining of bursa, joint or tendon sheath
**Diffuse-type**[††]: multinodular lesion involving a larger part or all of the synovial lining
**Articular involvement**
**Intra-articular**[$]: inside synovial lining of joint
**Extra-articular**[$$]: outside synovial lining of joint

**Both intra- and extra-articular**
**Cartilage-covered bone invasion**
**Yes**: clear invasion of bone invading cartilage; not only touch cartilage
**No**: no bone invasion or solely bone-usuration or bone invasion not cartilage-covered
**Muscular/tendinous tissue involvement**[*]
**Yes**: involvement of muscular/tendinous tissue or >180 degrees encasement of tendon/muscle
**No**: no involvement or encasement of tendon/muscle
**Ligament involvement**[**]
**Yes**: involvement of ligament or >180 degrees encasement of ligament
**No**: no involvement or encasement of ligament
**Neurovascular structure involvement**[#]
**Yes**: encasement >180 degrees of important nerves and/or vessels
**No**: no encasement of nerves or vessels

[†]**Localized-type**: be careful to always classify one nodular lesion as localized-type. Also when one nodular lesion is reeved by another structure (it might seem like additional nodules).
[††]**Diffuse-type**: be careful to always classify diffuse-type when two or more tendon sheaths or muscles are involved. Do not classify these cases as one large nodule.
[$]**Intra-articular**: concerning the knee: cruciate ligaments are counted as intra-articular structures as the synovial lining of the ligaments should be considered intra-articular.
[$$]**Extra-articular**: concerning the knee: Hoffa
[*] **Muscular/tendinous tissue involvement:** concerning the knee: also account parameter when solely popliteus muscle involvement is present.
[**]**Ligament involvement:** TGCT involvement of ligament, in hand or foot: account parameter when intra-tarsal/digital ligaments, ankle syndesmose and plantar fascia are involved. TGCT concerning the knee with ligament involvement: anterior and/or posterior cruciate ligament, and/or medial/lateral collateral ligament.
[#]**Neurovascular involvement**: in hand or foot: also digital or sensible nerves

# 4

# Treatments



# 5

# Pigmented villonodular synovitis: current concepts about diagnosis and management

FGM Verspoor, IC van der Geest, E Vegt, RP Veth, WTA van der Graaf, HWB Schreuder.

Future Oncology. 2013 Oct;9(10):1515-31.

## Abstract

At present, the treatment strategies in patients with localized and diffuse forms of pigmented villonodular synovitis have more or less been standardized. However, these strategies are not optimal because high recurrence rates persist and studies with a sufficient level of evidence are lacking. This systematic review article describes all known treatment options for intra-articular pigmented villonodular synovitis and their clinical results. Based on this research, we provide guidelines to support physicians in making the optimal treatment decisions. Given the rarity of the disease, randomized studies are not to be expected, but an international registry through existing networks would offer the benefit of getting a better insight into the outcome of this disease. Therefore, we propose a basic set of data to be investigated and ideally to be reported on in such a registry.

# Introduction

Pigmented villonodular synovitis (PVNS), also known as an intra-articular giant cell tumor, is a rare, benign and usually mono-articular lesion, arising from the synovial membrane. The lesion was first described in 1852 by the French surgeon Chassaignac, but he overstated its biological potential in referring to it as 'a cancer of the tendon sheath'.[7] The general accepted clinical description of PVNS was published by Jaffe *et al.* in 1941.[2] They reported 20 cases with joint and tendon involvement, and proposed a classification by location and histology.[2] The nomenclature outlined by Granowitz *et al.*[8] and modified by the WHO in 2002[9] is currently the most common one.

The pathogenesis of PVNS has been discussed for more than a century. Neoplastic, inflammatory, traumatic, metabolic and viral pathways were studied, but could not be confirmed until recently.[8] Studies found PVNS to be a neoplastic process with specific genetic changes and a reactive component known as the 'paracrine landscape effect'.[12,13,29] This new insight may lead to the development of treatment strategies, such as targeted therapy.[64,68]



PVNS affects adults predominantly between 20–50 years of age, with equal sex prevalence. The annual incidence has been estimated at 1.8 cases per million US inhabitants.[4,5] PVNS refers to articular involvement, which can be subdivided in a localized form (L-PVNS), characterized by discrete nodular or pedunculated lesions, and a diffuse form (D-PVNS), with involvement of the intra-articular soft tissue lining. The localized form rarely recurs after marginal surgical excision. The more common diffuse form recurs frequently and may result in a chronic disease, hampering normal function of the affected joint. Recurrence rates after treatment range from 9 to 46%, depending on the duration of follow-up and the joint involved.[3,50] Microscopically, the two forms are indistinguishable.[35]

Diagnosis of PVNS is often delayed due to the nonspecific nature of its symptoms.[3,4] At first the diagnosis was solely based on histology. At present, MRI is an indispensable tool in making a diagnosis, determining staging and evaluation during follow-up[31]. Despite these improvements in diagnostic options, limited progress has been achieved in the treatment of PVNS, particularly the diffuse form.[36,75] Physicians can choose from a number of treatment options with varying effectiveness and morbidity: a surgical synovectomy in an open or arthroscopic procedure, radiosynovectomy, external-beam radiotherapy (EBRT) or targeted treatments. Other treatments have also been described, such as cryosurgery, immunotherapy, arthroplasty, arthrodesis or amputation.[3,19,48-59,113]

Currently, no randomized trials comparing different treatment strategies are available; the highest level of evidence is level five, based on retrospective case series. These case series are difficult to compare because different disease locations,

subtypes, and primary and recurrent PVNS are all grouped together to increase patient numbers.[51,75] Various measurements are also used to assess treatment outcome.[41,44,51,55,60,114] We have systematically reviewed the original literature on PVNS. Based on this research we have formulated treatment guidelines. These guidelines can help clinicians in making consistent treatment plans for PVNS patients. In the future this would allow case series from different centers to be compared and analyzed together, resulting in a higher level of evidence for the optimal treatment of PVNS.

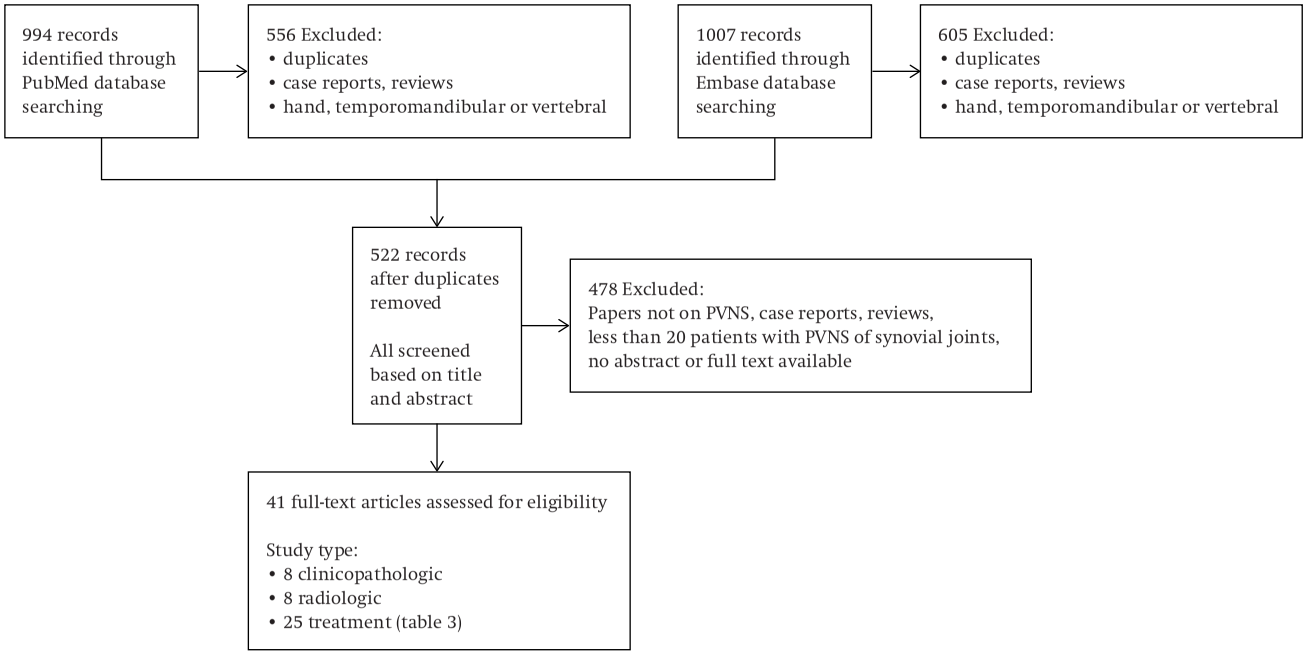
## Methods

Eligible papers were searched across a range of data sources, and included case series and clinical trials. Figure 1 shows a diagram of the search criteria and a selection of papers through the review process.

Search terms included 'pigmented villonodularsynovitis', 'villonodularsynovitis', 'PVNS', 'pigmented villo nodular synovitis', 'pigmented villonodular tenosynovitis', 'giant cell fibrohemangioma,' 'chronic hemorrhagic villous synovitis', 'fibrous xanthoma of synovium', 'pigmented villo nodular arthrosynovitis' and 'synovitis and pigmented villonodular'. PVNS of the hands, temporomandibular joint and spine, as well as single case reports and review articles, were excluded. PubMed, EMBASE and Cochrane databases were searched. To ensure that all appropriate references were identified, reference lists of retrieved articles were screened, and a general internet search using the above search terms for Google was undertaken to uncover any additional publications. No date limit was included. Papers were excluded if there was no abstract and/or full text available. All languages were included, and, if foreign, were translated.

The primary search yielded 840 articles. An initial screening of 522 titles and abstracts was undertaken after removal of duplicates, and any papers not meeting the broad inclusion/exclusion criteria (figure 1) were discarded. Forty-one papers reported on more than 20 cases or patients, of which 25 reported on treatment strategies. These 25 papers (tables 1 & 2) were read in full text, and data from these articles were systematically entered into a Microsoft® Office Access database (Microsoft Corporation, WA, USA). Data from each paper was categorized in relation to purpose and objectives, methodology, search, and analytical strategies, outcome and origins of the studies. In each article patient characteristics, subtype and locations of PVNS, number and types of treatments, number and kind of recurrences, duration of follow-up and number of patients lost to follow-up, other avail- able outcome measurements and treatment complications were scored. We attempted to pool and analyze patients from the selected articles. However, after

**Figure 1** Literature search strategy.




A search of PubMed and Embase covered all articles, with no new articles found using Google or reference lists. The Cochrane Database contained no articles on PVNS. The 25 key articles[3-5,19,35,36,39,41,44,50-52,54,55,74,75,115-123]. PVNS: Pigmented villonodular synovitis.

careful studying of all the literature, we were not able to identify patients treated in similar ways to make pooling justified. The described case series are too heterogeneous and there is a great diversity of patient groups. Furthermore, often operation techniques are not described in detail. Most articles do not describe how many surgeons performed the operation and how experienced they were. In our opinion, pooling data and analyzing it will not strengthen or change the found conclusions. To visualize this, we have attached tables (tables 1 & 2) that show this diversity of patients and treatments.

For some treatments, no case series over 20 patients were available. To enable completeness for these treatments, smaller series were included.

## Diagnosis

Based on clinical symptoms, age and history the diagnosis of PVNS is difficult. The disease mimics many other mono-articular pathologies, which makes differentiation a challenge.[31,60] L-PVNS can present with locking or clicking sensations of the affected joint.[4,8] D-PVNS is relatively painless, although it can cause discomfort and swelling.[3,4] In patients with knee complaints who undergo an arthroscopy, PVNS may be diagnosed macroscopically.[124]

MRI is an indispensable tool in PVNS, making diagnosis, staging and evaluation during clinical follow-up possible[31]. Hemosiderin deposition occurs in the majority of cases, but it is most prominent in the diffuse intra- articular form of the disease.[30] Hemosiderin is a magnetic material, its deposit on proliferative synovial tissue results in a spotty low signal or extensive low signal area within the proliferative synovial masses on T1- and T2-weighted images, which is best seen on fat-field echo sequence MRI images.[33] Fat-suppressed sequences obscured the deposit. This is highly diagnostic of PVNS. Enhancement of PVNS is common after intravenous administration of gadolinium; although the extent of enhancement varies, it is often a prominent feature.[30] The MRI features of PVNS include extent of synovial proliferation, joint effusion, erosion of bone, subchondral cysts, septations, cartilaginous defects and, in particular, the deposit of hemosiderin within the synovial masses.[31,33]

# Treatment strategies

## Surgical removal

### Localized disease

When diagnosed arthroscopically, L-PVNS can be excised immediately and completely if the tumor is clearly visible.[50,115] However, if the arthroscopist is not able to get an impression of the entire process, or if the tumor is difficult to reach, the procedure should be converted to an arthrotomy.[125] This can be done immediately in the same procedure or secondary after final diagnosis and staging with MRI.[30,111]

L-PVNS rarely recurs (0–15%) when completely resected.[3,5,19,52,54,116] The recurrence free survival rates for L-PVNS in large joints, at 1 and 5 years, were 100 and 88%, respectively, as reported by Chiari et al.,[75] while Sharma and Cheng calculated 2- and 5-year recurrence free survival rates of 91 and 73%, respectively.[36] Both studies included only primary cases. Besides recurrence rates, functional outcome (pain, swelling, range of motion and joint-specific scores) seemed improved. Byers et al.[3] reported 46% complete relief of symptoms postoperatively, compared with mostly 'excellent' and 'good' results in case series over the last three decades.[19,52,54,118] However, most reports on functional outcomes fail to define specific outcome measurements and are described in subjective terms. We found no literature on the treatment of L-PVNS recurrences, besides a few cases mentioned in larger series.[19]



### Diffuse disease

Unlike localized disease, D-PVNS is a much greater challenge to eradicate.[3,57,75] Despite many attempts to improve treatment strategies, recurrence rates have remained high (14–55%) over the last decade,[39,41,52,55,75,117,118] with a 5-year recurrence-free survival of 27–48% in large joints.[36,75]

In D-PVNS, removal of all the diseased tissue often means a complete anterior and posterior synovectomy as described by Chin et al. in patients with advanced primary and recurrent D-PVNS of the knee.[55] Currently, an open surgical synovectomy is considered more reliable compared with an arthroscopic synovectomy[51,55], especially in patients with large popliteal masses or extra-articular involvement[114]. It is technically almost impossible to remove all the pathologic tissue with an arthroscopic procedure. Blanco et al. suspects that many arthroscopic surgeons treating PVNS actually perform a subtotal (i.e., partial) synovectomy owing to the difficulty in visualizing the entire posterior aspect of the joint[39]. Ogilvie-Harris et al. describes complete arthroscopic synovectomies[52]. However, patients who had been selected for this arthroscopic procedure had no major posterior palpable masses and only slight or no radiographic degenerative changes.

**Table 1** Pigmented villonodular synovitis subtype, anatomical location, primary or recurrent disease with number of patients followed and duration of follow-up, in patients described in the selected articles.

| Study (year) | L-PVNS (n) | | | | | D-PVNS (n) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | K | H | A | O | T | K | H | A | O | T |
| Blanco et al. (2001) | – | – | – | – | – | 22 | – | – | – | 22 |
| Byers et al. (1968) | 13 | – | – | 33 | 46 | 24 | 2 | 5 | 3 | 34 |
| Chiari et al. (2006) | 9 | – | – | 14 | 23 | 3 | 3 | 3 | 10 | 19 |
| Chin et al. (2002) | – | – | – | – | – | 40 | – | – | – | 40 |
| de Visser et al. (1999) | – | – | – | – | 9 | – | – | – | – | 29 |
| Dines et al. (2007) | 84 | – | – | – | 84 | – | – | – | – | – |
| Flandry et al. (1994) | – | – | – | – | – | 25 | – | – | – | 25 |
| Flipo et al. (1994) | – | – | – | – | – | – | 58 | – | – | – |
| Heyd et al. (2010) | – | – | – | – | 1 | – | – | – | – | 40 |
| Johansson et al. (1982) | 7 | – | – | 4 | 11 | 24 | 4 | 2 | 3 | 33 |
| Liu et al. (2009) | 22 | – | – | – | 22 | – | – | – | – | – |
| Mankin et al. (2011) | – | – | – | – | – | – | – | – | – | – |
| Miller et al. (1982) | – | – | – | – | – | – | – | – | – | – |
| Myers et al. (1980) | 10 | – | – | – | 10 | 27 | 1 | 2 | 9 | 39 |
| Ogilvie-Harris et al. (1992) | 5 | – | – | – | 5 | 20 | – | – | – | 20 |
| Ottaviani et al. (2011) | 12 | – | – | 2 | 14 | 79 | – | – | 29 | 108 |
| Pavlica et al. (1997) | – | – | – | – | 30 | – | – | – | – | 20 |
| Pinaroli et al. (2006) | – | – | – | – | 8 | – | – | – | – | 20 |
| Rao et al. (1984) | 8 | – | – | – | 16 | 6 | – | – | – | 7 |
| Rochwerger et al. (1998) | 3 | – | – | – | 3 | 19 | – | – | – | 19 |
| Schwartz et al. (1989) | – | – | – | – | – | – | – | – | – | – |
| Sharma et al. (2009) | 12 | – | – | – | 12 | 37 | – | – | – | 37 |
| Ushijima et al. (1986) | – | – | – | – | – | – | – | – | – | – |
| Ustinova et al. (1986) | – | – | – | – | – | 18 | – | – | 6 | 24 |
| Wang et al. (2005) | – | – | – | – | 14 | | – | – | – | 14 |
| Total (n) | 199 | – | – | 53 | 308 | 358 | 68 | 12 | 60 | 550 |

Pigmented villonodular synovitis subtypes, anatomical locations, and primary or recurrent disease are often pooled in the literature to increase patient numbers.

† Both primary and recurrent patients, however, it is unclear how many of each there are.

A: Ankle; D-PVNS: Diffuse pigmented villonodular synovitis; FU: Follow-up; H: Hip; K: Knee; L-PVNS: Localized pigmented villonodular synovitis; NR: Not reported; O: Other joints; P: Patients with primary pigmented villonodular synovitis; R: Patients with recurrent pigmented villonodular synovitis; SD: Standard deviation of the mean; T: Total number of patients.

| L- and D-PVNS (n) | | | | | Primary/ recurrent | | FU (n) | Mean FU; months (range) |
|---|---|---|---|---|---|---|---|---|
| K | H | A | O | T | P | R | | |
| – | – | – | – | – | 22 | – | 14 | 33 (26–76) |
| 37 | – | – | – | 80 | – | – | 51 | (36–420) |
| 12 | 3 | 3 | 24 | 42 | 42 | – | 42 | 80 (26–294) |
| – | – | – | – | – | – | 40 | 40 | 60 (20–96) |
| 31 | 3 | 2 | 2 | 38 | 27 | 11 | 34 | 48 (12–228) |
| – | – | – | – | – | 84 | – | 26 | 66 (46–123) |
| – | – | – | – | – | 19 | 4 | 25 | 58 (20–126) |
| – | – | – | – | – | – | – | 56 | 34 (12–156) |
| 25 | 3 | 8 | 5 | – | 24 | 17 | 39 | (6–120) |
| 31 | 4 | 4 | 5 | 44 | – | – | 38 | 94 (7–192) |
| – | – | – | – | – | 22 | – | 19 | 22 (8–28) |
| 125 | 12 | 48 | 30 | 215 | – | – | 205 | NR |
| 18 | 8 | 3 | 7 | 34 | – | – | 32 | NR |
| – | – | – | – | – | – | – | 49 | NR |
| 29 | – | – | – | 29 | 29 | – | 25 | 54 (24–132) |
| 91 | 7 | 19 | 5 | 122 | † | † | 39 | 70 (SD: 51.6) |
| 34 | 1 | – | 1 | 50 | – | – | 22 | (3–132) |
| 25 | – | – | 3 | 28 | 28 | – | 28 | 97 (12–309) |
| 23 | 2 | 2 | 54 | 81 | – | 3 | 35 | D-PVNS: 24 (12–48)<br>L-PVNS: 43 (5–120) |
| 22 | – | – | – | 22 | – | – | 16 | 60 (24–192) |
| 75 | 20 | 2 | 2 | 99 | 58 | 41 | 99 | 162 (14.4–564) |
| 49 | – | – | – | 49 | 49 | | 49 | 74 (12–156) |
| 25 | 5 | 13 | 9 | 52 | – | – | 52 | NR |
| – | – | – | – | – | – | 14 | 24 | (6–72) |
| 15 | 13 | – | – | 28 | – | – | 28 | (12–144) |
| 695 | 81 | 104 | 147 | 1013 | 404 | 134 | – | – |

**Table 2** Various treatments or combination of treatments that pigmented villonodular synovitis patients received with available recurrence rates, described in the 25 selected articles.

| Study (year) | L-PVNS | | | | D-PVNS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AE | E | A | RR (%) | AS | OS | E | Des/ Amp | EBR | IS | A | X | RR (%) |
| Blanco et al. (2001) | – | – | – | – | K: 22† | – | – | – | K: 22† | – | – | – | 14 |
| Byers et al. (1968) | – | 13 | – | 15 | – | 16† | 9 | 4 | 2† | – | – | 1† | 46 |
| Chiari et al. (2006) | – | 27 | – | ‡ | – | 5† | 12 | – | – | – | 2 | 2† | ‡– |
| Chin et al. (2002) | – | – | – | – | – | 40† | – | – | 5† | 30† | – | – | 18 |
| de Visser et al. (1999) | – | 9 | – | 0.1 | – | 6 | 18 | – | – | 4 | 1 | – | 34§ |
| Dines et al. (2007) | 12 | 14 | – | 0 | – | – | – | – | – | – | – | – | – |
| Flandry et al. (1994) | – | – | – | – | – | 24 | 1 | – | – | – | – | – | 8 |
| Flipo et al. (1994) | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Heyd et al. (2010) | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Johansson et al. (1982) | – | 11 | – | 0 | – | 29 | – | – | – | – | 4 | – | K: 33<br>H: 50 |
| Liu et al. (2009) | 22 | – | – | 0 | – | – | – | – | – | – | – | – | – |
| Mankin et al. (2011) | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Miller et al. (1982) | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Myers et al. (1980) | – | 8 | – | NR | – | 12† | 18 | – | 3† | – | – | – | 18 |
| Ogilvie-Harris et al. (1992) | – | 5 | – | 0 | 11 | – | 9 | – | – | – | – | – | 30# |
| Ottaviani et al. (2011) | – | – | – | 26 | – | 73† | – | – | – | 73† | – | – | K: 30††<br>O: 9†† |

Shows the various different treatments pigmented villonodular synovitis patients received with their effect on recurrence rates. Notably, descriptions of recurrence rates are based on clinical, imaging or pathological confi med diagnosis.

† Some patients had a combination of these treatments.

‡ Chiari et al. [17]: 100% recurrence-free survival for L-PVNS at 1 year and 88% at 5 years; and 80% recurrence-free survival for D-PVNS at 1 year and 27% at 5 years. Sharma et al. [16]: 91% recurrence-free survival for L-PVNS at 2 years and 73% at 5 years; and 70% recurrence-free survival for D-PVNS at 2 years and 48% at 5 years.

§ Residual or recurrent disease.

¶ Joint replacement as necessary, no number or percentage mentioned.

# 9% RR for complete synovectomy and 56% for partial synovectomy.

†† Primary cases.

‡‡ Excisions, of which five were complete synovectomies and one was a menisectomy.

§§ Included all treatments of recurrent disease.

¶¶ Cumulative recurrence: 7% at 1 year, 15% at 5 years, 27% at 10 years, 31% at 15 years and 35% at 25 years.

| L- and D-PVNS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| AS | OS | E | Des/ Amp | EBR | IS | A | X | RR (%) |
| – | – | – | – | – | – | – | – | – |
| – | – | – | – | – | – | – | – | <50 |
| – | – | – | – | – | – | – | 24 | |
| – | – | – | – | – | – | – | – | – |
| – | – | – | – | – | – | – | – | – |
| – | – | – | – | – | – | – | – | – |
| – | – | – | – | – | – | – | – | – |
| – | 21† | 9 | – | 1 | 14† | 13 | 17† | 14 |
| – | 41† | – | – | 41† | – | – | – | 4.9 |
| – | – | – | – | – | – | – | – | – |
| – | – | – | – | – | – | – | – | – |
| – | – | 173 | 11 | 3 | – | 17 | 1 | 1.4 |
| – | – | 34 | – | – | – | ¶ | – | 0 |
| – | – | – | – | – | – | – K: 21 | – | 6 |
| – | – | – | – | – | – | – | – | – |
| K: 54† O: 17† | K: 33† O: 14† | – | – | – | K: 50† O: 23† | – | – | K: 55 O: 26 |

A: Arthroplasty; AE: Arthroscopic excision; AS: Arthroscopic synovectomy; D-PVNS: Diffuse pigmented villonodular synovitis; Des/Amp: Arthrodesis or amputation; E: Marginal excision, partial synovectomy (anterior or posterior) or subtotal synovectomy; EBR: External-beam radiotherapy; H: Hip; IS: Isotopes synoviorthesis; K: Knee; L-PVNS: Localized pigmented villonodular synovitis; O: Other joints; Op: Open surgical excision;
OS: Open complete surgical synovectomy or combined arthrotomy with arthroscopy; RR: Recurrence rate; X: Other treatments such as bone curettage, cup prosthesis, chemotherapy, menisectomy, bone impaction grafting, no treatment or unknown treatment.

The open synovectomy can be performed in one or two stages. To our knowledge, there is no literature that underlines the advantage of either a one- or a two-stage procedure. The two-stage procedure, with a few weeks rehabilitation between the anterior and posterior approach, may have the advantage of reducing wound surface and, therefore, functional impairment. Authors arguing for an open synovectomy state that this approach leads to longer hospital stays, longer rehabilitation periods and higher chances of postoperative stiffness that may require manipulation.[51-53] Although acceptable rates of recurrences in arthroscopic knee procedures were described, this was not verified by MRI, and was only based on clinical symptoms.[52,53,56] Recurrence rates up to 60% have been reported.[36,52,55,56] Theoretically, there is the risk of joint seeding and portal contamination during arthroscopic procedures[126], but experienced arthroscopists report recurrence rates of 9–20%[53], which is comparable to open procedures.[51,55] However, the level of 'experience' needed for these results and arthroscopic techniques are not specified.

A third option is to combine the open and arthroscopic procedures.[127] An arthroscopic approach offers excellent visualization of the anterior compartment, as well as the medial and lateral recesses. Combining this with an open posterior approach reduces the wound surface, which may result in better functional outcome and a similar risk of residual disease or relapse. Sharma et al. described that recurrence was highest in patients with diffuse disease who were treated with anterior arthroscopic surgery only, emphasizing the importance of eliminating posterior disease in D-PVNS as well as improving disease-free survival.[36]

### Arthroplasty

Total joint arthroplasty is frequently used in the treatment of severe primary PVNS, persistent recurrent PVNS or secondary osteoarthritis caused by PVNS.[50,111,114] Previously, patients with PVNS of the hip were observed until total joint arthroplasty became necessary. This is no longer recommended, since early complete synovectomy of the hip can postpone the need for an arthroplasty. Luxation of the femoral head, to achieve a complete synovectomy, is not advisable. It can cause avascular necrosis by interruption of the vascular supply to the femoral head. Total hip arthroplasty can be necessary when the bone is excessively affected by erosions.[58,59] Studies show a potential lower recurrence rate after complete synovectomy combined with total hip replacement than after complete synovectomy only.[50,111] An extensive exposure of the joint, as achieved in joint replacements, ensures complete debridement of the synovial membrane. In the knee this can be obtained by excision of the posterior cruciate ligament.[128] Hamlin et al.[129] described 14 D-PVNS patients, 11 of which had active disease and were treated with total synovectomy and total knee arthroplasty.[128] Three polycentric and 11 condylar prostheses were used. Of the condylar implants, nine were inserted

with cement, one with hybrid fixation (the femoral component was inserted without cement and the tibial component with cement) and one without cement. Ten patients had an intact, well-functioning prosthesis at an average follow-up evaluation of 10.6 years (range: 3.6–20.1). Of the four failures, three had aseptic loosening requiring revision. There were two recurrences of PVNS, one eventually requiring an above the knee amputation. To our knowledge, there is no evidence on how often patients need a joint replacement after synovectomies. Some authors mention arthroplasty for a few patients (table 2). However, they mostly do not clarify if this was required for extensive disease or secondary osteoarthritis caused by progressive disease or multiple treatments.

Thus, a prosthesis can provide a painless, well-functioning extremity in a patient who would otherwise have had complaints of stiffness and pain.[129] Since the incidence of post-operative complications of prostheses surgery has decreased remarkably, this treatment has been applied more frequently.[3,59] Prosthesis surgery can be used as a primary modality to treat PVNS-induced osteoarthritis, or in conjunction with synovectomy in severe or persistent recurrent PVNS to achieve radical disease removal.



## Additional treatments

Complete resection of D-PVNS is almost never possible. Therefore, additional treatments may be useful to reduce functional impairment of joints, residual disease and recurrences. These additional treatments can be used directly as initial adjuvant treatment with the intention of reducing the risk of recurrence, or only applied when recurrences occur as another treatment option. Various additional treatments have been described.

### Cryosurgery

Cryosurgery, in the form of liquid nitrogen spray, is widely used as an adjuvant treatment in various tumors.[130] Mohler and Kessler treated three D-PVNS patients through open synovectomy plus cryosurgery, two with recurrent and one with arthroscopically unresectable disease.[49] All non-cartilaginous surfaces were treated with cryosurgery. There were no complications or morbidity from the cryosurgical procedure and patients had excellent functional recovery. After 14, 30 and 31 months there were no clinical symptoms of recurrence.

Described complications of cryosurgery in the treatment of benign and low-grade malignant bone tumors are: infections (4%) caused by tissue necrosis; damage to the articular (cartilage) surface; temporarily nerve palsy; and, sporadically, a gas embolism.[131]

The effectiveness of cryosurgery in the treatment of primary severe or recurrent PVNS, has not currently been tested. So, if applied this should be performed in the setting of a clinical trial, by an experienced surgeon.

### External-beam radiotherapy

Differences of opinion exist on the role of EBRT in the treatment of PVNS. It seems to be reserved for treatment of extensive extra-articular involvement of the disease near vital structures such as the neurovascular bundle, residual disease after complete synovectomy and persistent recurrent disease.[39,40] Blanco et al. described 22 patients with primary D-PVNS who received an anterior arthroscopic synovectomy followed, 2 weeks later, by EBRT.[39] Nineteen patients (86%) had excellent or good results after an average follow-up of 33 months (range: 26–76), with three (14%) clinical recurrences. Ustinova et al. treated 24 D-PVNS patients with adjuvant EBRT after incomplete surgical disease removal.[118] Of these, 18 patients had D-PVNS affecting the knee joint and six of these had bone involvement. The surgeons performed a complete synovectomy followed by EBRT within 3–4 weeks. After a follow-up ranging from 0.5–6 years, complete recovery convalescence was noted in 23 patients and occupational rehabilitation was achieved in 21 patients. These data indicate a high efficacy of surgical removal combined with EBRT. A multicenter study by Heyd et al. presented 41 cases, 24 primary cases and 17 recurrences.[120] All 41 followed patients received surgical synovectomy plus EBRT. Excellent and good results were achieved in 34 patients (87%), with a recurrence rate of 5% during a 0.5–10-year follow-up period. During the last decade, other smaller case series confirmed the positive results of adjuvant EBRT with regards to local recurrence and functional outcome of PVNS[40,128]. Currently, total doses in the range of 30–36 Gy are recommended.[47] To our knowledge, there is no clinical trial available regarding the optimal time frame for EBRT after surgery. The abovementioned studies used 2–4 weeks.[39,118]

Reported complications associated with EBRT are skin reactions, poor wound healing, joint stiffness, sarcomatous transformation, femoral fractures and impotence.[3,120] Owing to these complications, EBRT should not be used as a primary treatment, but only for symptomatic residual and recurrent PVNS. However, one needs to be reserved when recommending EBRT for this benign condition, especially in young patients.

### Radiosynovectomy

Radiosynovectomy (isotopic synoviorthesis) has been a focus of discussion for years. It is mostly used as an adjuvant treatment after surgical synovectomy, but no large series have been published in which it is systematically compared with surgery alone or with other adjuvant therapies. Chin et al. treated 40 patients with

primary and recurrent D-PVNS of the knee.[55] All were treated by open surgical synovectomy. Thirty patients received additional intra-articular radiation synovectomy with use of 11 GBq of dysprosium-165 in combination with 20 mg triamcinolone hexacetonide to decrease the swelling that is commonly associated with this procedure. Five patients received additional EBRT of 35 Gy in single fractions each day over a 15-day period. The overall recurrence rate, detected by MRI, was seven out of 40 patients (18%), during the 5-year follow-up. The reason why some people received radiosynovectomy and others received no additional treatment or EBRT was not stated. Owing to the lack of randomization and the small number of patients in the group that had received no adjuvant treatment or EBRT, no fair comparison is possible. In the authors' opinion, complete resection of all PVNS tissue is the key factor in preventing recurrences. The largest case series on radiosynovectomy is a single-center report of Ottaviani et al. describing 108 cases of D-PVNS and 14 of L-PVNS.[41] In their center, all patients who were not treated elsewhere before (n = 73) were treated by open synovectomy with additional radiosynovectomy (knees with 185 MBq of yttrium-90; hips and ankles with 111 and 74 MBq of rhenium-186, respectively). They encountered no serious complications and only mild febrile reactions. Relapse rates of these patients were 15 out of 50 (30%) for knees and two out of 23 (9%) for other locations, after a mean follow-up period of 4.6 years. The remaining patients, who had relapsed after treatment elsewhere, received only surgery. A direct comparison between these two groups was not performed because relapsed patients are at higher risk for another relapse.[41] A few smaller studies (ten patients or less) reported recurrence rates of 0–17% after surgery and adjuvant yttrium-90 radiosynovectomy using higher doses (555–925 MBq).[46,132]

Other small case series (five to ten cases per series) reported on PVNS that recurred after surgery, and was subsequently treated only by radiosynovectomy. In these patients, who were at a higher risk of another relapse, success percentages of approximately 50% were described.[19,133,134]

Severe complications, such as radionecrosis requiring plastic surgery and chronic severe pain have incidentally been described, particularly in ankles with limited soft tissue coverage[135]. Osteonecrosis and intra-articular infections have been described following radiosynoviorthesis in osteoarthritis and arthroplasty.[136] Theoretically, radiosynovectomy may carry a risk of radiation-induced malignancy, but this has never been reported. Furthermore, in theory it has the disadvantage of not covering extra-articular disease. In general, the side effects are mild, especially if radiosynovectomies are performed by an experienced team and necessary precautions are taken.[41]

A study investigating the efficacy and articular effects of radiosynovectomy in patients with persistent arthritis of the knee showed that radiosynovectomy with

yttrium-90 combined with triamcinolone hexacetonide was no more effective than triamcinolone hexacetonide alone.[137] Furthermore, harmful effects on human cartilage and bone following radiation synovectomy with yttrium-90 were reported, both in vivo and in vitro.[138,139] Owing to these findings, we discourage the use of radiosynovectomy for PVNS treatment, or if continued it should be in the setting of a proper randomized trial.

**Immunotherapy**

Some research uses anti-TNF-α as a local or general treatment in patients with relapsing PVNS, with relatively good results.[29,48,140] Kroot reported a patient with recurrent PVNS of the knee, which clinically improved after TNF-α blockade.[48] In addition, a marked reduction in macrophages and TNF-α expression in the synovium was found. Fiocco et al. reported two patients with recurrent disease of the knee who benefited from the TNF- α blocker etanercept.[141] Knee function and disease activity improved, which was confirmed by regression of knee joint synovial proliferation. The use of anti-TNF-α is supported by the fact that macrophages and proinflammatory cytokines, such as TNF-α are present in the synovium of patients with PVNS.[142] This treatment is possibly an option in patients who relapse frequently, but it is not validated. Furthermore, this may be replaced by upcoming results of targeted therapy (see 'Targeted therapy' section).

**Targeted therapy**

The search for the pathogenesis of PVNS has led to the development of new treatment options, such as targeted therapy.[68] PVNS is a benign neoplastic process with specific genetic alterations.[12,13] A specific t(1;2) translocation, involving the COL6A3 gene (on chromosome 2q35) and the M-CSF gene (also known as CSF1, on chromosome 1p13), is present in a fraction of tumor cells in PVNS/tenosynovial giant cell tumors (TGCTs).[143] This fusion gene, t(1p13;2q35), encodes for a fusion protein, which attracts non-neoplastic cells expressing M-CSFR, though a 'paracrine landscape' effect.[12,13] It is hypothesized that CSF inhibitors, such as imatinib, may disrupt this paracrine land- scape effect found responsible for PVNS/TGCT growth.[12,13,144]

Imatinib has been reported to block M-CSFR activation at therapeutic concentrations.[145] Rapid relapse at discontinuation, and a secondary response obtained after imatinib reintroduction was reported in gastrointestinal stromal tumors.[146] The same effect was described after treatment of two cases of PVNS with imatinib, one in an elbow[143] and one in a hip[147]. PVNS relapsed after interruption of treatment, and when imatinib was reintroduced a second remission was observed.[143] Cassier et al. described the largest retrospective study of 29 imatinib-treated PVNS/TGCT patients.[64] Most patients (20 out of 29; 69%) had undergone previous surgery.

Four of the nine remaining patients received imatinib mesylate as neoadjuvant therapy before they underwent surgical excision. Cassier et al. do not differentiate their results for the two disease entities. Overall, one (4%) patient was in complete remission, four (15%) were in partial remission and 20 (74%) patients had stable disease. Remarkably, two (8%) patients had metastatic disease, and both progressed. In two (8%) patients, evaluation was not possible due to discontinuation of treatment due to early side effects (febrile neutropenia and grade 3 edema). Although these findings are promising, there are disadvantages to imatinib treatment: it has to be given chronically, since probably PVNS recurs after discontinuation, and it is not without side effects. These mainly include hematologic and gastrointestinal toxicity.[148] Another disadvantage is that prolonged exposure may cause new mutations, which are imatinib resistant.[149] Theoretically, this may lead to more aggressive PVNS subgroups or worse, secondary malignant tumors.



In the abovementioned study by Cassier et al., over half the patients (17; 59%) discontinued imatinib treatment due to side effects during the mean 10.8-month follow-up (range: 3.0–42.9).[64] This percentage is much higher than observed in metastatic gastrointestinal stromal tumors treated with imatinib. At present, the results of an international study with nilotinib are awaited. Of note, neither imatinib nor nilotinib are specific CSF1R inhibitors.

Another important clinical issue is the goal of CSF inhibition treatment in PVNS. Is it a merely palliative treatment or is meant for bridging until surgery or radiation therapy? Does it induce long-term complete remission and what is the ideal duration of treatment?

At this moment, CSF1R inhibitors should be preserved for patients with unresectable disease or multiple recurrences that produce clinical and functional impairment.

## Follow-up

MRI has been shown to be an effective tool for detection of D-PVNS tissue preoperatively and for monitoring patients postoperatively.[60,113] MRI is highly sensitive, but less specific for detecting residual PVNS postoperatively, owing to the confounding presence of surgical changes within the knee. Chin *et al.* advised a postoperative MRI after 3 and 6 months, then annually (it was not specified for how many years).[55] However, 3 months after surgical treatment early postoperative changes may still be present. We recommend a MRI, 6 months postoperatively, as a baseline scan to observe changes when symptoms arise. This can be after a long period of time, as PVNS can recur after many asymptomatic years. No evidence exists that an annual MRI is contributory in the absence of clinical symptoms.

Each treatment increases the risk of functional impairment and secondary osteoarthritis in addition to all abovementioned complications.[3,4,19,39,51,54,55,75,117]

The socio-economic consequences of the multiple operations and adjuvant treatments for PVNS are seldom described; Ustinova *et al.* described some patients that could not continue their work owing to the consequences of D-PVNS.[118]

Several groups have been looking for predictive markers for possible PVNS relapse[150,151], but none have yet been found. However, in a small number of long-term follow-up studies evaluating the different types and locations of PVNS, more recurrences were seen in the diffuse form, in large joints and in prior incomplete synovial excisions.[3-5,75]

Using joint-specific scores, Enneking et al.[152] and Chiari et al.[75] showed that prevention of recurrence does not automatically equate to a successful clinical outcome. de Visser et al. evaluated the functional aspects of treatment of PVNS and found excellent or good results despite 34% residual and recurrent disease.[19] Consequently, PVNS research should focus more on the effects of the disease and treatments on joint function.

Longer-term follow-up studies would not only increase our understanding of the biological behavior of PVNS, but would also enable us to evaluate the potential development of secondary osteoarthritis.[116] It could provide more knowledge on the lifespan of prostheses after complete synovectomy. Furthermore, we should pay greater attention to the impact of PVNS on patients' occupational and social lives. PVNS can be highly debilitating and, thus, can have a major impact on quality of life. More knowledge of these aspects can contribute greatly to patient counseling.

## Literature limitations

Our literature search on PVNS treatment options yielded mostly retrospective case series. However, instead of clarifying, they provided new uncertainties. First, since PVNS rarely occurs, the major subgroups, localized and diffuse are often merged (table 1)[4,35,44,50,74,121-123]. It has been known for decades that these two entities behave different biologically.[2] Second, the anatomic site of PVNS can have a significant influence on its clinical behavior.[2,8,59] According to Chung and Janes, bone invasion is more likely to occur in joints without large synovial recesses to accommodate expanding synovial masses, such as the hip.[58] Furthermore, owing to the deeper location the diagnosis may be delayed. Schwartz et al. found higher recurrence rates in affected knees compared with any other locations.[50] Nevertheless, subtypes and locations are combined in outcome measurements to increase patient numbers (table 1).[3,19,44,50,75,120] Third, the diversity in treatment options is enormous (table 2). In most case series, more than three different treatment strategies are described.[3,19,44,50,54,75,117] In this way, the already mixed patient groups are too small to draw conclusions from. Fourth, patient groups consist of newly diagnosed patients and patients already treated elsewhere (table

1).[5,19,41,50,51] Some studies focus on this topic and describe the treatments patients received before arrival in their center,[19,50,51,55] and others do not report the composition of their patient groups at all.[3,44] It leads to bias in outcome measurements, such as overall recurrence rates, which becomes incorrectly high compared with case series with solely primary cases. Schwartz et al. described this manipulation as referral bias, mostly present in patient populations from tertiary centers.[50] Their study showed that patients with previous surgery had more recurrences than those who did not ($p < 0.01$). The patients with previous procedures had unusual cases of PVNS: their prior operations may have affected recurrence in some way, perhaps by biologically aggressive characteristics or locations less amenable to eradicate surgically.

Besides the abovementioned difficulties, other issues should be highlighted. What is the best way to describe treatment outcome? Studies used recurrence rates, recurrence-free survival percentages, numbers of secondary osteoarthritis and rate of complications, while some only used broad outcome terms such as good, excellent, fair and poor. Unfortunately, the largest case series (>20 patients) all use different outcome measures or are incomplete in their descriptions (figure 1).

Some studies accept clinical symptoms and radiographs to detect recurrent disease[3,5] and others insist on MRI or even histological con- formation before designating a relapse. Only a few differentiate between residual disease and recurrences.[19,117] Again, a decision needs to be made whether clinical symptoms are enough proof, or if MRI and histological conformation are required. What treatment implications do residual or recurrent disease on MRI without clinical symptoms have? Should additional treatment occur, or is 'wait and see' sufficient? Further research needs to provide these answers. In addition, clear differentiation between real recurrent disease and additional operations for other reasons is significant. Not all operations in one joint indicate recurrent PVNS. Frequently, it is secondary osteoarthritis requiring arthroplasty or stiffness needing manipulation under anesthesia.

Finally, follow-up time is usually short; especially knowing PVNS can recur after many years.[59] Due to the retrospective character of these studies, data are missing and a high number of patients are lost to follow-up.

We emphasize the weakness of the current study, because it is based on the only available literature, which has the above described limitations. However, by pointing out these limitations, future studies may be able to gather stronger evidence on PVNS.

## Guidelines

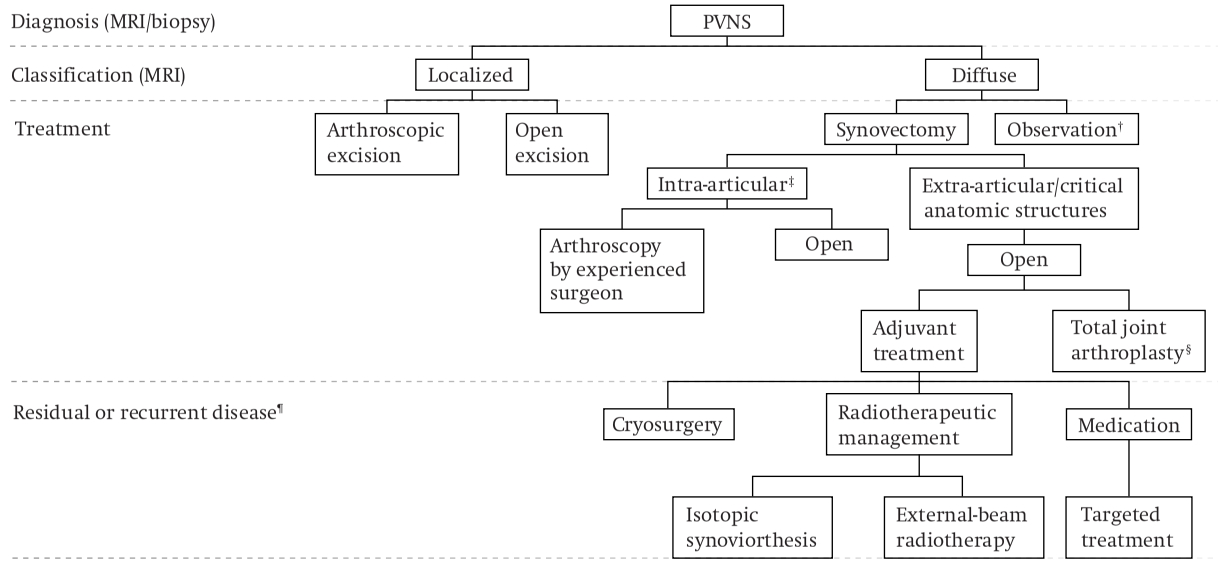
The following guidelines are summarized in figure 2. After diagnosis by histology and/or MRI, correct classification (localized or diffuse) determines the best individualized treatments. PVNS behaves differently in various locations. The limited available literature describes mostly treatment results on knees and hips. These guidelines are, therefore, most reliable for these joints, but in our opinion applicable to all joints. In primary L-PVNS, arthroscopic excision is sufficient. Open excision should be preserved for difficult excisable L-PVNS lesions. For recurrent L-PVNS the results of excision are unknown. Due to the good results of primary surgery[116], we recommend re-excision for symptomatic recurrent disease.

D-PVNS is clearly more difficult to treat with higher recurrent rates and various treatment options sparse in evidence of efficiency. The treatment of choice is surgical synovectomy. According to the extent of the process, the involved anatomical structures, and the experience of the surgeon, an open or an arthroscopic approach needs to be considered. The main goal of treatment is the removal of all abnormal synovial tissue, thereby taking away the source of symptoms, and reducing joint destruction and recurrences. Based on present knowledge and technical operative possibilities, complete arthroscopic removal of D-PVNS tissue should be reserved for patients with limited, intra-articular disease and an experienced arthroscopist. When it is uncertain whether all the diseased tissue has been removed, or there is disappointing visibility, the closed procedure should be converted to an open procedure. In patients with extra-articular involvement or large popliteal masses, an arthroscopic approach is contra-indicated, but can be combined with an open approach.[52,56,57,113] Importantly, these patients should be referred to centers with expertise in this disease from the time of diagnosis. Adjuvant treatment is applied in cases of residual disease. In case of recurrent disease, the patient will require rescue therapy or second- or third-line treatment.

If there is residual disease after surgical excision adjuvant treatment needs consideration. The strongest available evidence on treatment effects favor EBRT. All other adjuvant treatments; cryosurgery, radiosynovectomy and immunotherapy, lack evidence on treatment effects and outcome caused by the abovementioned literature limitations. Targeted therapy with the tyrosine kinase inhibitor, imatinib, has shown promising results in some patients, but this treatment is still in an experimental phase and imatinib is not believed to be as effective as CSF1R-directed treatment. Additionally, it is unclear which patients benefit, how long they should be treated and whether side effects of this and other tyrosine kinase inhibitors may hamper long-lasting treatment of this in general benign disease.

Arthroplasty is preserved for severe primary or recurrent PVNS where removal

**Figure 2** Proposed treatment algorithm for pigmented villonodular synovitis.




Blue boxes: proposed diagnostic and treatment pathway for PVNS. Red box: no longer an acceptable option.
† Observation until total joint arthroplasty becomes necessary is no longer recommended.
‡ Combined anterior arthroscopic and posterior open surgery may be an option; however, only if all PVNS tissue is accessible and only in trials.
§ Total joint arthroplasty is indicated in severe primary PVNS, persistent recurrent disease or end-stage osteoarthritis.
¶ Preferably, patients with residual or recurrent disease should be treated in clinical trials to obtain evidence. PVNS: Pigmented villonodular synovitis.

of menisci, collateral and cruciate ligaments is needed to achieve excision of all pathologic tissue. In most of these cases bone erosion and degenerative joint disease is present. Here, arthroplasty facilitates a functional joint. The kind of prosthesis best applied, a regular prosthesis or megaprosthesis used for tumor surgery, depends on the extension of tissue removal.

Clearly, all adjuvant treatments should be given in a trial to generate stronger evidence for future guidelines. These trials should be limited to one or two treatments to gather enough evidence on efficacy, but also on complications, side effects, joint function and quality of life (box 1). The decision concerning diagnostics, treatment and follow-up should ideally be made in a multi-disciplinary team of people who have expertise in this peculiar and rare disease.

## Conclusion & future perspective

An international registry should be started in which group registries could enter their data. This would enable the start of future protocols based on greater patient numbers. It should answer questions about the percentage of patients with residual, recurrent or degenerative disease based on clinical, imaging or pathological data. Centralization of treatments for PVNS patients will lead to less morbidity and a decrease in residual and recurrent disease. It will improve the quality and quantity of treatments. For example, future arthroscopic techniques, along with greater experience, will allow greater and more complete access to intra-articular pathologic tissue. As in all technical procedures, there is a definite learning curve to a complete arthroscopic synovectomy. We may become able to excise more severe PVNSs arthroscopically.

Arthroplasty as a treatment of PVNS should be studied further, including the risk of prosthesis loosening caused by persistent or recurrent disease. Furthermore, the significance of cryosurgery, EBRT, radiosynovectomy, immunotherapy and targeted therapy in the treatment of PVNS should be elucidated. Indications for each therapy must be clarified, including their optimal regimes. The discovery of an aggressive biological subgroup would be helpful in decisions about the need for additional treatments, for example, a specific patient group experiencing favorable effects with targeted therapy.

More knowledge should become apparent about the impact of PVNS on patient's quality of life, influenced by the disease itself or by multiple received treatments. This will not only optimize care, but it will also improve patient education and guidance.

Despite the benign character, PVNS patients' lives are often severely affected in their quality due to the long course of the disease, the multiple surgeries, residual- or post-surgical complaints and secondary osteoarthritis. Although the two forms, L-PVNS and D-PVNS, are almost identical histologically, elimination of

D-PVNS is much more challenging. Various different treatment options have been proposed and implemented, however, due to the low incidence of the disease, randomized clinical trials are lacking and treatment efficacies are hard to compare. Analyses and comparisons of different case studies are difficult and may lead to inaccurate conclusions. Nevertheless, we have now established treatment guidelines based on a systematic analysis of the literature to improve future comparability and aggregation capabilities of study results from different centers. The gold standard of treating D-PVNS is complete surgical synovectomy. Other therapeutic options, preserved for severe primary and recurrent disease, are treatments with additional cryosurgery, arthroplasty or adjuvant EBRT. In case of relapsed disease radiosynovectomy, immunotherapy with TNF-α blockers or CSF1R-directed targeted therapy, preferably in the context of a well-designed clinical trial, are proposed. These trials would ideally be initiated internationally in order to reach a significant number of patients in a short period of time. This has already been the case in the first studies with nilotinib [101,102]. Outside clinical trials it would be interesting to make use of networks, such as the World Sarcoma Network, to create a registry in which international outcome data can be linked to each other [103]. This will generate data that will certainly improve the outcome of this rare and disabling disease.



**Websites:**

[101] ClinicalTrials.gov. Nilotinib in Patients With Relapsed or Metastatic Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor/Diffuse-Type Giant Cell Tumor. http://clinicaltrials.gov/ct2/show/ NCT01207492

[102] ClinicalTrials.gov. Study of Nilotinib Efficacy in Pigmented Villo-Nodular Synovitis/ Tenosynovial Giant Cell Tumour (PVNS/TGCT). http://clinicaltrials.gov/ct2/show/NCT01261429?recr=Open&cntry3=EU%3AGB&phase=1&lup_s=04%2F19%2F2012&lup_d=360

[103] World Sarcoma Network. www.worldsarcomanetwork.com/

**Box 1 Key points for analyzing case series.**

***Diagnosis through MRI and/or histology***

- Differentiate in all analyses
  - PVNS (intra-articular) from tenosynovial giant cell tumor (extra-articular)
  - Localized PVNS from diffuse PVNS
  - Anatomical locations
  - Primary from recurrent PVNS
  - Accidental PVNS (e.g., during prostheses surgery)

***Treatment***

- Localized PVNS
  - Excision/nodulectomy
  - Arthroscopic or open surgery
- Diffuse PVNS
  - Number and nature of treatments in which (tertiary) center
  - Surgical synovectomy
    - Complete or partial
    - Open or arthroscopic
  - Prostheses
  - Additive treatments
    - Cryosurgery
    - Radiosynovectomy
    - External-beam radiotherapy
    - Immunotherapy
    - Protein kinase inhibitor
  - Time to first recurrence
  - Number of manipulations
  - Number and kind of treatments elsewhere

***Follow-up***

- Mean overall follow-up: date of diagnosis to date of last follow-up
- Mean follow-up: date of first operation in tertiary hospital (index operation) to date of last follow-up
- Number of overall recurrences
- Number of recurrences in tertiary hospitals
- Number of nonrecurrence operations (e.g., prostheses for secondary osteoarthritis)
- Nature of relapse: MRI, clinical symptoms, histological proven
- Recurrence-free survival (1 ,5 ,10 or 15 years)
- Pre- and post-operative joint function score (Knee Society Score, Western Ontario and McMaster Universities Arthritis Index, Harris Hip Score)
- Number and nature of complications
- Quality of life (RAND-36 and CIS20r)
- Number of patients lost to follow-up with reasons (explanation)

CIS20r: Checklist Individual Strength; RAND-36: RAND 36-item Health Survey; PVNS: Pigmented villonodular synovitis.

## Executive summary

***Background***

- Limited progress has been achieved in the treatment of pigmented villonodular synovitis (PVNS), particularly the diffuse form.
- Currently, the highest level of evidence on treatment outcomes is level five, based on retrospective case series.

***Diagnosis***

- MRI is an indispensable tool in diagnosing, staging and evaluating in clinical follow-up.

***Treatment strategies***

- Surgical removal
  - Localized PVNS can be excised immediately and completely if the tumor is clearly visible on arthroscopy. If one is unable to get an impression of the entire localized PVNS process, or if the tumor is difficult to reach, the procedure should be converted to an arthrotomy.
  - In diffuse PVNS, surgical removal of all diseased tissue often means a complete anterior and posterior synovectomy.
  - According to the extent of the process, the involved anatomical structures and the experience of the surgeon, an open or an arthroscopic approach needs to be considered.
  - Complete arthroscopic removal of diffuse PVNS tissue should be reserved for patients with limited, intra-articular disease and an experienced arthroscopist.
  - If there is extra-articular involvement or large popliteal masses an arthroscopic approach is contraindicated, but can be combined with an open approach.
- Arthroplasty
  - Total joint arthroplasty is used in the treatment of severe primary PVNS, persistent recurrent PVNS or secondary osteoarthritis caused by PVNS.

***Additional treatments***

- Cryosurgery
  - Cryosurgery should be preserved for severe primary and recurrent disease in a study.
- External-beam radiotherapy
  - External-beam radiotherapy should be reserved for treatment of extra-articular involvement, residual disease after complete synovectomy and persistent recurrent disease.
- Radiosynovectomy
  - The use of radiosynovectomy for PVNS treatment should be discouraged, or if continued, should be used in the setting of a proper randomized trial.
- Immunotherapy
  - In the case of PVNS relapse, immunotherapy with TNF-α blockers can be considered, preferably in the context of a clinical trial.
- Targeted therapy
  - Currently, CSF1R inhibitors should be preserved for patients with unresectable disease or multiple recurrences that produce clinical and functional impairment.

***Follow-up***

- An MRI 6 months postoperatively can be useful as a baseline scan to observe changes when symptoms arise.
- Each treatment increases the risk of functional impairment and secondary osteoarthritis.
- Prevention of recurrence does not automatically equate to a successful clinical outcome.

***Literature limitations***

- The highest level of evidence is level five, based on retrospective case series.
- Case series are difficult to compare because different disease locations, subtypes, primary and recurrent PVNS are grouped to increase patient numbers.
- Various measurements are used in case series to assess treatment outcomes.
- Case series have a relatively short follow-up time.
- Case series differ in or lack description of recurrent or residual disease.

***Future perspective***

- In the future, predictive markers for possible PVNS relapse could be developed.
- Centralization of care would improve PVNS outcomes.
- More knowledge of the lifespan of prostheses after complete synovectomy would also be useful.
- The impact of PVNS on patients' occupational and social lives should be studied, because PVNS can be highly debilitating and, thus, have a major impact on quality of life.
- An international registry would enable the start of future protocols based on greater patient numbers in a short period of time.

# 5

# 6

# Arthroplasty for tenosynovial giant cell tumors

## *17 patients followed for 0.2-15 years*

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## Abstract

Tenosynovial giant cell tumors (t-GCTs) can behave aggressively locally and affect joint function and quality of life. The role of arthroplasty in the treatment of t-GCT is uncertain. We report the results of arthroplasty in t-GCT patients.

t-GCT patients (12 knee, 5 hip) received an arthroplasty between 1985 and 2015. Indication for arthroplasty, recurrences, complications, quality of life, and functional scores were evaluated after a mean follow-up time of 5.5 (0.2–15) years.

2 patients had recurrent disease. 2 other patients had implant loosening. Functional scores showed poor results in almost half of the knee patients. 4 of the hip patients scored excellent and 1 scored fair. Quality of life was reduced in 1 or more subscales for 2 hip patients and for 5 knee patients.

In t-GCT patients with extensive disease or osteoarthritis, joint arthroplasty is an additional treatment option. However, recurrences, implant loosening, and other com- plications do occur, even after several years.

## Introduction

Tenosynovial giant cell tumors (t-GCTs) are benign proliferative growths of the synovial membrane.[1] The approximate annual incidence in the USA is 1.8 patients per million inhabitants.[4] T-GCT mainly affects adults between 20 and 50 years of age, with the same prevalence in both sexes. There is a predilection for weight-bearing extremities, the knee and the hip being the most commonly involved.[42]

The clinical presentation is non-specific, with mild discomfort, stiffness, effusion, or progressive pain. Based on the clinical and radiological presentation, 2 subtypes of t-GCT have been identified, localized t-GCT (Lt-GCT) and diffuse t-GCT (Dt-GCT).[30,42]

Treatment strategies are based on removal of all pathological tissue. In primary, limited disease, a surgical synovectomy is often sufficient.[76] However, for extensive or recurrent disease, complete surgical synovectomy can be a technical challenge. Recurrence rates have been reported to be between 0% and 15% for Lt-GCT and between 9% and 46% for Dt-GCT, depending on the duration of follow-up and on the joint involved.[42,75,116]



A variety of treatment modalities in addition to surgical resection of t-GCT have been used to achieve cure, such as external beam radiation therapy, radiation synovectomy, cryosurgery, immune or targeted therapy, and joint arthroplasty. However, little is known about the actual effect of these additional treatments.[76]

The surgical removal of t-GCT combined with arthroplasty has been described previously in patients with extensive disease, and in patients with destructive joint changes caused by the disease itself or by the multiple treatments patients received.[129] The goal of this treatment is to achieve a disease-free, well-functioning joint.[153] In addition, patients with osteoarthritis-like symptoms in whom t-GCT was an incidental finding during arthroplasty have been described.[59]

This retrospective study was conducted to analyze the results of arthroplasty in patients with t-GCT. More specifically, we examined the indications, number of recurrences, complications, quality of life, and joint function in relation to t-GCT subtype and the joint affected.

## Patients and methods

For this retrospective study, we identified 141 t-GCT patients in our patient databases (1985–2015). 48 patients were classified as Lt-GCT and 93 as Dt-GCT. 17 of these patients (5 Lt-GCT and 12 Dt-GCT) received an arthroplasty (tables 1 and 2).

Clinical, pathological, radiological, treatment, and follow-up information were assessed by 2 independent reviewers (FGMV and AS). Any disagreements were

resolved by consensus with a third reviewer (HWBS). Recurrences, treatment complications, functional scores, and quality of life (QoL) were documented according to t-GCT subtype and location. During the regular hospital visits, QoL questionnaires were used and function scores were taken.

QoL was evaluated by using the Dutch translation of a generic QoL instrument, the 36-item Short Form health survey (SF-36)[154] and the 20-item Checklist Individual Strength (CIS20r) questionnaire.[155] 14 patients participated, and the other 3 patients were lost to follow-up. 1 patient did not complete all the questions in the CIS20r questionnaire, so it could not be used.

Scoring systems used to evaluate function were the standardized Western Ontario and McMaster Universities osteoarthritis index (WOMAC)[156], the Knee Society score (KSS)[157], and the Harris hip score (HHS)[158]. The data were extracted from database records. We managed to collect function scores from all but 1 patient.

### Ethics

The study protocol (2012/555) was assessed by our institutional review board (the research ethics committee of the Radboud University Nijmegen Medical Centre) and was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees.

## Results

### Hip

5 patients received a hip arthroplasty. 4 had Dt-GCT and 1 had Lt-GCT. 2 were women aged 20 and 25 years and 3 were men aged 36, 44, and 49 years. The indication for total hip arthroplasty (THA) was extensive disease (n = 3) and secondary osteoarthritis (n = 1). In the fifth patient, Lt-GCT was an incidental finding. The mean overall follow-up after arthroplasty was 8.6 (7–15) years (table 1).

3 primary patients received their arthroplasty within 1.5 years of diagnosis (table 1). 1 patient with recurrent disease had a surgical synovectomy followed by an unsuccessful yttrium radiosynovectomy elsewhere. 4 years after diagnosis, this patient was treated at our tertiary center using a 3-stageprocedure. During almost 15 years of follow-up, no recurrences or complications occurred (tables 1 and 2).

Another patient who was initially treated using a 3-stage procedure for extensive disease (table 2) first had an anterior luxation immediately after THA with acetabular bone impaction grafting, followed by a cup revision after a trauma 5 years later (without any evidence of recurrent disease), and finally had histologically proven recurrent disease 4 years after that. This recurrent disease

was treated with a synovectomy, additional cryosurgery, and removal of osteosynthesis material that had been placed during the initial THA (table 2).

### Quality of life

An SF-36 score was obtained for 4 of the 5 patients, on average 10 (6–15) years after arthroplasty. 2 patients scored low (> 1 SD below the means for the general population[155]) on Vitality and General health perception and 1 of these 2 patients also scored low on Physical functioning, Social functioning, Role limitations due to physical problems, General mental health, and Bodily pain (table 3, see Supplementary data).

CIS20r was obtained for 4 patients, on average 10 (6–15) years after arthroplasty. Compared to healthy individuals[155], 1 patient scored high (> 1 SD above healthy individual means) on all 4 domains: Fatigue, Concentration, Motivation, and Physical activity (table 4, see supplementary data).

### Function scores

A Harris hip score was obtained for all 5 THA patients, on average 6.8 (4–13) years after arthroplasty. 4 patients scored excellent (90–99) and 1 patient scored fair (77) (Table 5, see Supplementary data).

## Knee

12 patients, 4 with Lt-GCT and 8 with Dt-GCT, received a knee arthroplasty, 6 women (mean age 58 (48–63) years) and 6 men (mean age 54 (33–73) years). Indications for arthroplasty were extensive disease (n = 6), secondary osteoarthritis (n = 3), and an incidental finding (n = 3) (Tables 1 and 2). The mean overall follow-up period after arthroplasty was 5.5 (0.2–13) years (Table 1).

Patient 7 (Lt-GCT) received a total knee arthroplasty (TKA) for osteoarthritis almost 7 years after diagnosis of t-GCT. Rehabilitation was complicated by stiffness, which was treated by manipulation under anesthesia. 2 other patients with osteoarthritis received a TKA, 8 and 38 years after diagnosis of Dt-GCT.

The 6 patients who were treated for extensive disease received an arthroplasty on average 9 (1.6–17) years after diagnosis (Table 1). These patients had 0–4 recurrences before arthroplasty and 1 recurrence diagnosed by ultrasound after TKA with so far no intervention. 2 patients suffered postoperative complications after TKA. 1 patient had neuropathic pain, which was treated with surgical neurolysis (figure 1). Another patient experienced stiffness, which was treated by manipulation under anesthesia. This last patient also developed medial tibial component loosening 6 years after arthroplasty, followed by revision surgery. No recurrent disease, polyethylene wear, or infection was found.

**Table 1** Details of t-GCT patients treated with arthroplasty: demographics, indications, recurrences and time of follow up

| ID | Gender | Age at diagnosis (yrs) | Type t-GCT | Side | FU (yrs) prior to arthroplasty | N previous recurrence(s) |
|---|---|---|---|---|---|---|
| ***Knee*** | | | | | | |
| 5 | F | 55 | Diffuse | L | 7.5 | 4 |
| 7 | F | 41 | Localized | L | 6.8 | 0 |
| 22 | F | 61 | Localized | L | 0 | 0 |
| 32 | F | 44 | Diffuse | R | 8.4 | 2 |
| 40 | M | 38 | Diffuse | L | 17.4 | 2 |
| 44 | F | 60 | Diffuse | L | 1.6 | 0 |
| 56 | F | 47 | Diffuse | R | 16.2 | 1 |
| 69 | M | 62 | Localized | R | 0 | 0 |
| 75 | M | 28 | Diffuse | R | 8.1 | 1 |
| 105 | M | 73 | Localized | L | 0 | 0 |
| 120 | M | 24 | Diffuse | R | 37.9 | 1 |
| 132 | M | 30 | Diffuse | R | 3.2 | 3 |
| ***Hip*** | | | | | | |
| 1 | M | 44 | Diffuse | R | 0.5 | 1 |
| 3 | M | 34 | Diffuse | R | 1.5 | 1 |
| 34 | V | 24 | Diffuse | R | 0.7 | 1 |
| 92 | M | 49 | Localized | R | 0 | 0 |
| 115 | V | 16 | Diffuse | R | 4.3 | 2 |

TKA= total knee arthroplasty, PF= patella femoral arthroplasty, HP= hemi arthroplasty knee, THA= total hip arthroplasty.
The follow-up prior to arthroplasty was defined as the period between first pathologic conformation of diagnosis and arthroplasty. The follow up after arthroplasty was defined as the period between arthroplasty and most recent patient contact. Time to recurrence after arthroplasty was calculated as the time from joint arthroplasty until histological proven recurrent disease, or highly susceptive recurrent disease on ultrasound.

## Quality of life

SF-36 was obtained for 10 patients, on average 4.6 (0.2–11) years after arthroplasty. 5 patients scored low (> 1 SD below the means for the general population) on General health perception; 4 on Physical functioning, Role limitations due to physical problems, Vitality, and Health change; 3 on Social functioning, General mental health, and Bodily pain; and 2 on Role limitations due to emotional problems (table 3, see supplementary data).

CIS20r was obtained for 9 of the patients, on average 4.6 (0.2–11) years after arthroplasty. Compared to healthy individuals[155], 2 patients scored high (> 1 SD above

| Indication for arthroplasty | Age at prosthesis (yrs) | Implant | FU (yrs) after arthroplasty | N Recurrence(s) after arthroplasty |
|---|---|---|---|---|
| Extended disease | 62 | TKA | 5.9 | 1 On ultrasound |
| Osteoarthritis | 48 | TKA | 3.3 | 0 |
| Incidental | 61 | PF | 8.3 | 0 |
| Extended disease | 52 | TKA | 0.2 | 0 |
| Extended disease | 56 | TKA | 3.5 | 0 |
| Extended disease | 62 | TKA | 5.3 | 0 |
| Extended disease | 63 | TKA | 5.4 | 0 |
| Incidental | 62 | TKA | 12.9 | 0 |
| Osteoarthritis | 36 | PF | 10.8 | 0 |
| Incidental | 73 | HP | 6.3 | 0 |
| Osteoarthritis | 62 | TKA | 2.3 | 0 |
| Extended disease | 33 | TKA | 2.1 | 0 |
| Extended disease | 44 | THA | 10.7 | 1 Histological confirmed |
| Extended disease | 36 | THA | 8.4 | 0 |
| Osteoarthritis | 25 | THA | 7.0 | 0 |
| Incidental | 49 | THA | 10.7 | 0 |
| Extended disease | 20 | THA | 14.6 | 0 |



the means for healthy individuals) in all 4 domains, i.e. Fatigue, Concentration, Motivation, and Physical activity, and 1 patient scored high on the Motivation and Physical domains (table 4, see supplementary data).

### Function scores

WOMAC[156] and KSS[157] were obtained for all but 1 patient, at an average of 3.7 (0.2–11) years after arthroplasty. According to the standardized WOMAC sum scores (0–100), higher values indicate less pain, less stiffness, or better physical functioning.[159] 2 knee patients scored below 50 on all subscales. 3 other knee patients had less than 70 in the total score; in particular, they had low scores on the Stiffness and Physical functioning subscales. On the KSS Object knee score, 7 patients had excellent results (80–100), 1 had good results (70–79), and 3 had poor results (< 60). On the KSS Function knee score, 6 patients had excellent results (80–100) and the other 5 patients had poor results (< 60), as with the low WOMAC scores in these 5 patients (table 6, see supplementary data).

**Table 2** All treatments t-GCT patients received before and after arthroplasty, including complications and implant information.

| | | Treatments | | |
|---|---|---|---|---|
| ID | **Center** | **1e** | **2e** | **3e** |
| ***Knee*** | | | | |
| 5 | Referred | SE[a] + ME | SE | Two stage |
| 7 | Primary | Nodulectomy | Arthrotomy* | Arthroscopy* |
| 22 | Primary | Patella fracture → OSM | **PF**[i] | |
| 32 | Primary | 2-stage | SE | SE +**TKA** |
| 40 | Referred | SE | SE | 2-stage + Cryo + **TKA** |
| 44 | Primary | SE + **TKA**[c] | MUA* | Revision tibia* |
| 56 | Primary | SE | SE + **TKA** | |
| 69 | Referred | **TKA**[i] | | |
| 75 | Referred | Yttrium | 2-stage | **PF*** |
| 105 | Referred | **TKA**[i] | | |
| 120 | Primary | SE | Yttrium | **TKA*** |
| 132 | Referred | SE | SE | SE + Yttrium |
| ***Hip*** | | | | |
| 1 | Primary | 3-stage + Cryo + **THA**[h] with acetabular BIG | Cup revision*j | SE + Cryo + remove OSM |
| 3 | Referred | SE with luxation | **THA** | |
| 34 | Primary | SE | **THA*** | |
| 92 | Referred | **THA**[i] | | |
| 115 | Referred | SE | Yttrium | 3-stage + Cryo + **THA** |

SE= surgical synovectomy, ME= partial meniscectomy, OSM= osteosynthesis material, TKA= total knee arthroplasty (i= incidental finding), PF= patella femoral arthroplasty, HP= hemi arthroplasty knee, THA= total hip arthroplasty *= treatment not for recurrent disease, 2-stage= an anterior synovectomy followed by a posterior synovectomy 4-6 weeks later, 3-stage= a complete synovectomy followed by a second look with excision of residual disease and arthroplasty in a 3rd procedure, Cryo= per operative additional cryosurgery, BIG= Bone impaction grafting, Yttrium= radiosynovectomy with Yttrium, MUA= manipulation of the knee under anesthesia, RT= external beam radiation therapy, PS = posterior stabilized, PFC= patella

| | | Implant information | |
|---|---|---|---|
| 4e | 5e | Implant | Type of implant |
| SE + Cryo + RT | **TKA** | PS, PFC, cemented | PFC ® SIGMA ®<br>TC3 Knee System - DePuy Synthes |
| **TKA**[c, *] | MUA* | PS, cemented | PFC ® SIGMA ®<br>TC3 Knee System - DePuy Synthes |
| | | PF, cemented | Smith & Nephew<br>pat-mod III long femoral |
| neurolyse* | | PS, PFC, cemented | PFC ® SIGMA ®<br>TC3 Knee System - DePuy Synthes |
| | | PS, cemented | PFC ® SIGMA ®<br>TC3 Knee System - DePuy Synthes |
| | | CR, cemented | PFC ® SIGMA ®<br>TC3 Knee System - DePuy Synthes<br>With extended stem tibia (3cm) |
| | | PS, PFC, cemented | PFC ® SIGMA ®<br>TC3 Knee System - DePuy Synthes |
| | | CR, PFC, cemented | Genesis II prosthesis |
| | | PF, cemented | Smith & Nephew<br>pat-mod III long femoral |
| | | HP, cemented | Oxford |
| | | PS, PFC, cemented | PFC ® SIGMA ®<br>TC3 Knee System - DePuy Synthes |
| Imatinib no response | SE + **TKA** | PS, PFC, cemented | Nexgen |
| | | THA, BIG, cemented | Exeter stem, contemporary cup,<br>bone allograft, mesh, Kreutzschale |
| | | THA, cemented | Exeter stem, contemporary cup |
| | | THA, BIG, cemented | Exeter stem, contemporary cup,<br>bone allograft |
| | | THA, cemented | Exeter stem, contemporary cup |
| | | THA, uncemented | Link screw in cup MP ® reconstruction<br>prosthesis |

femoral component, CR= Cruciate retaining. Perioperative complications included; delayed wound healing[a], stiffness[c], neurolysis[e], hip luxation[h], traumatic cup displacement[j].
Primary patients received all treatments at our institution; referred patients had their initial treatment(s) elsewhere. A three stage procedure in hip joint patients implies a complete synovectomy, followed by a second look with excision of residual disease and arthroplasty in a third planned procedure. For the knee a two stage procedure starts with an anterior synovectomy, followed by a posterior synovectomy four to six weeks later.

**Figure 1** Gradient-echo-based MRI image from a patient with recurrent t-GCT (right knee).

There was very low signal intensity corresponding to hemosiderin depositions anterior to the lateral meniscus, extending to the infrapatellar fat pad. Furthermore, there was a hemosiderin deposition in the recessus lateralis posterior to the lateral femoral condyle. These localizations corresponded to recurrent Dt-GCT, which was confirmed by surgical removal.

# Discussion

## Indications

In this study, t-GCT patients with extensive disease and/or degenerative joint disease following treatment(s) were eligible for arthroplasty. Also, there were patients who were preoperatively assumed to have osteoarthritis which (during operation) turned out to be t-GCT. Other authors have found similar indications for arthroplasty in t-GCT patients.[30,160,161] Furthermore, unusual cases of t-GCT first presenting after TKA have been described.[160,162]

In general, patients with t-GCT in the hip received their arthroplasty over 20 years earlier than patients with t-GCT of the knee. An explanation for this age difference might be that lesions involving the hip joint are associated with a higher incidence of bony erosion and cyst formation compared to those involving the knee. Some investigators have hypothesized that the smaller intra-articular space in the hip does not allow the tumor to expand without causing increased pressure on the femoral and acetabular cartilage.[76]

THA has been performed in young patients, with good results. However, the authors of a long-term follow-up evaluation of THA advised caution with this procedure in younger patients because of high failure rates.[163]

## Recurrences

2 recurrences were found in our patient group; both of these Dt-GCT patients were treated for extensive disease. The recurrence after THA was histologically proven. The recurrence after knee arthroplasty was diagnosed and followed on ultrasound. There have been case reports of recurrent t-GCT being diagnosed with arthroscopy or during revision arthroplasty.[162] However, with the improved visualization of periprosthetic soft tissues on MRI, diagnosis of recurrent t-GCT after total joint arthroplasty should no longer be a difficulty.[164]

Gitelis et al.[165] reported on 28 patients in whom synovectomy was combined with hip arthroplasty (15 cup arthroplasties, 10 THAs, and 3 hemiarthroplasties—1 of which was subsequently converted to a THA). The average follow-up time was 3.6 years, with 1 recurrence.

In our study, the 2 recurrences occurred 6 and 9 years after arthroplasty, indicating that the number of recurrences may increase further with longer follow-up times. These 2 patients with recurrent disease had a staged procedure before arthroplasty. In hip arthroplasty, clearance of diseased tissue was done before implantation, to minimize the chance of recurrent disease. However, 1 of the 2 hip patients who underwent a staged procedure showed recurrent disease. A meta-analysis of t-GCT in hips showed a recurrence rate of 4% with surgical synovectomy and total joint arthroplasty as compared to a rate of 28–50% after treatment with surgical synovectomy alone. The indication for additional arthroplasty depended on the extent of disease and on cartilage damage.[59]

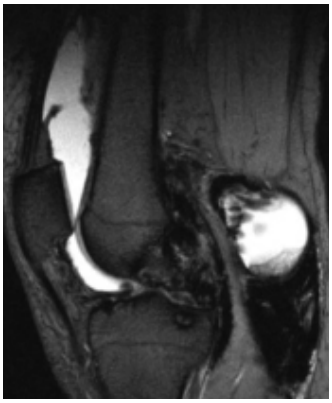
With extensive Dt-GCT, extra-articular lesions are often encountered, e.g. in the head of one of the gastrocnemius muscles (figure 2). In these cases, all pathological tissue should be removed before joint arthroplasty, to reduce the risk of residual and/or recurrent disease. To ensure removal of all pathological tissue, before arthroplasty a staged procedure should be considered in these difficult-to-cure patients.

## Complications

We had 2 cases of aseptic loosening 5 and 6 years after arthroplasty, but not recurrent disease. Hamlin et al.[129] (1998) described 18 patients who underwent TKA, 14 with Dt-GCT and 4 with Lt-GCT. There were 3 cases of aseptic loosening, 1 of them with recurrent disease. Another patient with recurrent disease needed an above-the-knee amputation.

Other complications, such as stiffness requiring manipulation and neuropathic pain requiring neurolysis, have been reported in patients undergoing arthroplasty.[166] However, this patient group is possibly more prone to develop these kinds of complications from limited joint function preoperatively, due to the disease itself or to previously received treatments.[42]

**Figure 2** Gradient-echo-based MRI image from a patient with recurrent t-GCT (left knee).



There was very low signal intensity corresponding to hemosiderin depositions, particularly in the posterior compartment of the joint and in the popliteal fossa. There was also osseous destruction.

## Quality of life

In 5 patients, we found reduced QoL scores compared to the general population.[154] Recently, 2 other publications had QoL scores for t-GCT patients[20,42] but these scores were not reported for t-GCT patients treated with arthroplasty.

## Joint function

We found reduced joint function after arthroplasty in 5 of the 12 t-GCT knee patients, mainly due to stiffness (table 6, see supplementary data). It has been reported that preoperative joint function is a predictor of postoperative TKA function.[167] In general, reduced preoperative joint function in t-GCT patients is related to disease severity or the often multiple treatments in the past.[75] Similar results have been reported for postoperative hip function.[168] However, 4 out of 5 of our hip arthroplasty patients had excellent Harris hip scores. Gitelis et al.[165] reported that after an average follow-up of 5 years, 24 of 28 patients treated with primary hip arthroplasty had satisfactory results and 4 had poor results. The poor results were due to mechanical failure of the implants.[165]

Our hip arthroplasty patients had better function scores than our knee patients, which might be explained by their younger age and shorter course of disease. Taking disease-induced loss of joint function into consideration, joint function outcomes may be better with earlier joint arthroplasty. It may also reduce the chances of recurrent t-GCT, as the disease is less extensive and therefore easier to eradicate. However, early joint arthroplasty might result in higher revision rates.

## Limitations

The retrospective character of this study, the small number of patients, the different indications for arthroplasty, and the different implants used should not go unnoticed. It is difficult to perform a prospective study with adequate patient numbers, because of the low incidence of t-GCT and the years of delay before local recurrence may occur. Complete information regarding subtypes, location, arthroplasty, and other treatments was available, including long-term follow-up. Because of this, the information could possibly be used in future (meta-)analyses to obtain evidence regarding arthroplasty in the treatment of t-GCT. Furthermore, patients with localized t-GCT as an incidental finding should be differentiated from those with diffuse recurrent and extensive t-GCT, as localized disease behaves less aggressively.

It should also be noticed that QoL and function scores were taken at variable points after arthroplasty. To our knowledge, this is the first study to report QoL measures in t-GCT patients who underwent arthroplasty. QoL is important in a disease as disabling as t-GCT. Further studies should investigate whether or not the reduced QoL in this specific patient group is a consequence of the disease itself, of the arthroplasty, of the (multiple) treatment(s) received, or of other factors, such as comorbidities or issues not related to disease.

In summary, in t-GCT patients with extensive disease or osteoarthritis, arthroplasty is an additional treatment option after surgical synovectomy. However, recurrences, implant loosening, and other complications do occur, even after years of follow-up.

**Table 3** Quality of life in SF-36 scores for t-GCT patients after arthroplasty.

| ID | Follow-up (yrs) after arthroplasty | SF-36 scores Physical functioning | Social functioning | Role physical | Role emotional | Mental health | Vitality | Bodily pain | General health | Health change |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Knee*** | | | | | | | | | | |
| 5 | 4.0 | 90 | 100 | 100 | 100 | 72 | 60 | 67.4 | 85 | 50 |
| 7 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 22 | 5 | 70 | 100 | 0 | 100 | 56 | 35 | 32.6 | 45 | 50 |
| 32 | 0.2 | 25 | 0 | 0 | 66.7 | 72 | 75 | 10.2 | 60 | 25 |
| 40 | 7.8 | 85 | 100 | 75 | 100 | 80 | 55 | 67.4 | 30 | 25 |
| 44 | 4.4 | 45 | 100 | 100 | 100 | NA | 35 | 79.6 | 45 | 50 |
| 56 | 5.4 | 85 | 100 | 100 | 100 | 84 | 70 | 100 | NA | 50 |
| 69 | 4.0 | 70 | 87.5 | 100 | 100 | 88 | 60 | 79.6 | 70 | 100 |
| 75 | 10.8 | 35 | 25 | 0 | 0 | 24 | 25 | 32.6 | 0 | 25 |
| 105 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 120 | 2.3 | 35 | 25 | 0 | 0 | 28 | 40 | 44.9 | 15 | 25 |
| 132 | 2.1 | 95 | 100 | 75 | 66.7 | 80 | 65 | 67.4 | 55 | 50 |
| ***Hip*** | | | | | | | | | | |
| 1 | 10.2 | 90 | 100 | 100 | 100 | 76 | 75 | 69.4 | 50 | 50 |
| 3 | 6.3 | 100 | 100 | 100 | 100 | 76 | 25 | 100 | 50 | 50 |
| 34 | 7.0 | 100 | 100 | 100 | 100 | 88 | 90 | 100 | 90 | 50 |
| 92 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 115 | 14.6 | 40 | 37.5 | 0 | 100 | 56 | 40 | 10.2 | 50 | 50 |
| General population means (SD) | | 81.9 (23.2) | 86.9 (20.5) | 79.4 (35.5) | 84.1 (32.3) | 76.8 (18.4) | 67.4 (19.9) | 79.5 (25.6) | 72.7 (22.7) | 52.4 (19.4) |

SF-36= the 36-item Short Form Health Survey, NA= not available. A low score indicates a score >1SD below general population means.

**Table 4** Quality of life in CIS20r scores at the last follow up, for t-GCT patients after arthroplasty.

| ID | Follow-up (yrs) after arthroplasty | CIS20r Fatigue | Concentration | Motivation | Physical | Total |
|---|---|---|---|---|---|---|
| ***Knee*** | | | | | | |
| 5 | 4.0 | 8 | 5 | 4 | 3 | 20 |
| 7 | NA | NA | NA | NA | NA | NA |
| 22 | NA | NA | NA | NA | NA | NA |
| 32 | 0.2 | 27 | 12 | 13 | 21 | 73 |
| 40 | 7.8 | 21 | 8 | 4 | 10 | 43 |
| 44 | 4.4 | 18 | 5 | 21 | 11 | 55 |
| 56 | 5.4 | 9 | 5 | 4 | 5 | 23 |
| 69 | 4.0 | 9 | 5 | 4 | 4 | 22 |
| 75 | 10.8 | 50 | 30 | 23 | 17 | 120 |
| 105 | NA | NA | NA | NA | NA | NA |
| 120 | 2.3 | 33 | 21 | 13 | 13 | 80 |
| 132 | 2.1 | 17 | 11 | 4 | 3 | 35 |
| ***Hip*** | | | | | | |
| 1 | 10.2 | 18 | 10 | 8 | 9 | 45 |
| 3 | 6.3 | 16 | 5 | 5 | 4 | 30 |
| 34 | 7.0 | 12 | 5 | 4 | 7 | 28 |
| 92 | NA | NA | NA | NA | NA | NA |
| 115 | 14.6 | 45 | 19 | 18 | 18 | 100 |
| Healthy individuals mean (SD) | | 17.3 (10.1) | 9.5 (5.0) | 7.9 (4.1) | 6.6 (4.5) | 41.5 (19.8) |

CIS20r= 20-item Checklist Individual Strength questionnaire, NA= not available. High scores (>1SD above healthy individual means) indicate a high level of fatigue, a high level of concentration problems, low motivation and a low level of physical activity.

**Table 5** Joint function in HHSs for t-GCT patients after hip prosthesis implantation.

| ID | Follow-up in years after arthroplasty implantation | Harris Hip Score Total |
|---|---|---|
| 1 | 7.9 | 90 |
| 3 | 6.3 | 95 |
| 34 | 4 | 95 |
| 92 | 9.9 | 99 |
| 115 | 12.5 | 77 |

In the Harris Hip Score (HHS), activities of daily living and gait account for 47 points, pain for 44, joint movement for 5 and absence of deformity for 4 in a total of 100. Harris defined 90 to 100 points as excellent, 80 to 90 as good, 70 to 80 as fair and below 70 as poor.

**Table 6** Joint function in WOMAC and KSS scores for t-GCT patients after knee arthroplasty.

| | Follow-up (yrs) | WOMAC | | | | KSS | | |
|---|---|---|---|---|---|---|---|---|
| ID | FU post | Pain | Stiffness | Physical | Total | Object | Function | Total |
| 5 | 4.0 | 75 | 75 | 76.5 | 76.0 | 87 | 80 | 167 |
| 7 | 1.7 | 65 | 62.5 | 85.3 | 79.2 | 84 | 90 | 174 |
| 22 | 0.5 | 70 | 75 | 69.1 | 69.8 | 71 | 55 | 126 |
| 32 | 0.2 | 70 | 50 | 57.4 | 59.4 | 53 | 40 | 93 |
| 40 | 6.8 | 95 | 100 | 98.5 | 97.9 | 94 | 100 | 194 |
| 44 | 5.3 | 75 | 50 | 66.2 | 66.7 | 88 | 40 | 128 |
| 56 | 3.0 | 100 | 100 | 88.2 | 91.7 | 93 | 80 | 173 |
| 69 | 4.0 | 85 | 75 | 88.2 | 86.5 | 84 | 90 | 174 |
| 75 | 10.8 | 30 | 0 | 22.1 | 21.9 | 53 | 50 | 103 |
| 105 | NA | NA | NA | NA | NA | NA | NA | NA |
| 120 | 2.3 | 45 | 37.5 | 47.1 | 45.8 | 53 | 50 | 103 |
| 132 | 2.1 | 95 | 75 | 95.6 | 93.8 | 94 | 100 | 194 |

NA= not available, WOMAC= standardized Western Ontario and McMaster Universities Osteoarthritis Index, KSS=Knee Society Score. In the standardized WOMAC (0-100) sum scores, higher values indicate less pain, stiffness or better physical functioning. On the KSS scores were defined excellent (80-100), good (70-79), fair (60-69) or poor (<60).

# 6

# 7

# Cryosurgery as additional Treatment in Tenosynovial Giant Cell Tumors

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## Abstract

Tenosynovial giant cell tumors (TGCT) emerge from the synovium and can behave aggressively. Surgical resection is the standard treatment. However, up to half of the patients with diffuse-type show recurrences. Several additional treatments have been applied to reduce recurrences, none of these treatments was proven to be superior to surgical resection solely. This article describes the results of additional cryosurgery to surgical resection.

We retrospectively evaluated 141 TGCT patients, between 1999 and 2007. Twelve patients had additional cryosurgery. The knee (n=8), hip (n=2), ankle (n=1) and elbow (n=1) were affected. Primary outcome variables were treatment indications, recurrences and complications.

Indications for additional cryosurgery were extended disease, bone involvement and surgical key locations difficult get disease free. Five patients had recurrent disease, all of which had prior treatments. None of the primary treated patients had recurrent disease. One patient had a deep infection.

Cryosurgery may serve as an additional treatment for diffuse TCGT in selected cases. However, because of the small number of patients and the heterogeneous group we could not prove an advantage of additional cryosurgery over surgical resection only. Cryosurgery should be considered for further evaluation in a prospective study. If there is any effect it would be helpful, especially in patients with multiple TGCT recurrences.

## Introduction

The tenosynovial giant cell tumor (TGCT), formerly known as pigmented villonodular synovitis (PVNS), is a rare proliferative disorder originating from the synovial membrane. Its annual incidence is described as 1.8 per million US citizens.[4] TGCT has a neoplastic origin, with a reactive component based on specific genetic changes.[9,12] Although TGCT can behave locally aggressive, it is considered a benign disorder.[9] Two subtypes have been described, 1), the less aggressive, localized form (LTGCT), which usually is a single nodular lesion, and 2) the diffuse form (DTGCT), which usually affects the whole joint and frequently recurs (14-55%).[41,76] The knee (75%) is the most frequently affected joint, followed by the hip, ankle, elbow and other synovial joints.[9]

The recommended treatment for TGCT is surgical resection of all affected tissue.[76] Incomplete resection or multiple treatments can result in functional impairment.[11] With extended or recurrent disease, several additional treatments (e.g. External Beam Radiotherapy (EBRT), radiosynovectomy, immune and targeted therapy) have been applied to reduce recurrence rates.[76] None of these treatments was proven to be superior to surgical resection on its own, which makes aggressive, persistently recurrent TGCT difficult to cure.[76]



Cryosurgery, in the form of liquid nitrogen spray, is widely used as an additional treatment for various bone tumors.[131] In order to try to reduce recurrence rates, we started using cryosurgery as an additive treatment to surgical resection of TGCT in selected cases. Mohler and Kessler[49] reported on the successful treatment of three TGCT patients through surgical synovectomy combined with cryosurgery. To the best of our knowledge, there are no other publications that describe cryosurgery as an additive treatment to surgical resection, in the treatment of TGCT.

We retrospectively evaluated TGCT patients treated with cryosurgery in addition to surgical synovectomy, with respect to the indication for additional treatment(s), the number of recurrences and complications.

## Materials and methods

We retrospectively searched pathologic and radiologic reports in the hospital database with the keywords 'pigmented villonodular synovitis', 'local tenosynovitis', and 'giant-cell tumor of the tendon sheath'. Between 1985 and 2014, 141 TGCT patients were identified; 48 (34%) with localized and 93 (66%) with diffuse disease. According to operative reports, cryosurgery was used in 12 patients, between 1999 and 2007. Clinical, pathological, radiological, treatment and follow up information was obtained from medical records. The study protocol (CMO2015-1915) was

assessed by our institutional review board (the research ethics committee of the Radboud University Nijmegen Medical Centre) and was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

There was no protocol for the use of additional cryosurgery. All patients with extended or recurrent disease were discussed in a multidisciplinary team (medical oncology, radiotherapy, surgical oncology, orthopedic surgical oncology). However, eventually it was the surgeon's call for each individual case whether or not to use cryosurgery. In the 12 patients that received additional cryosurgery the knee (n=8), hip (n=2), ankle (n=1) and elbow (n=1) were affected. All diagnoses were histologically confirmed. One patient (elbow) had localized disease; all other patients had diffuse disease. The mean age at the time of cryosurgery was 39 (range 21-61) years. All patient characteristics are listed in table 1.

Cryosurgery was used in addition to a surgical synovectomy. After complete removal of the affected tissue, the non-cartilaginous surface of the joint (synovium, joint capsule, bone) was treated with three cycles of liquid nitrogen spray. All frozen tissue got to at least -50°C. Spontaneous thawing warmed the tissue up to 20°C. After three cycles of rapid cooling and spontaneous thawing the entire wound was lavaged with sodium hyponitrate to prevent seeding of tumor cells. A healthy circulation (no use of a tourniquet) is important to protect neurovascular structures and the skin.[131,169] To our knowledge there is no literature available yet on costs of cryosurgical treatment. However, we would estimate a maximal extra surgical time of 15 minutes (i.e. three times 5 minutes, quick freeze and slow thawing). The materials needed for cryosurgery are a little container and temperature sensors. Liquid nitrogen costs 10 euro cents a liter and we use less than a liter for one patient. Details of all received treatments are listened in table 1.

Between 1985 and 2014 our follow up protocol has changed from an intensive follow up with 3 monthly visits, including a MRI every 6 months, to only a single clinical follow up visit 3 months postoperatively with additional visits when clinical symptoms appear, a 'wait and see policy'.

Outcomes were the indications for additional cryosurgery, recurrent disease and complications. To be able to formulate indications for cryosurgery we scored extra-articular disease, large expansion (described in operative reports as; extensive or bulky disease or when two or more compartments of the knee were involved), bone involvement and involvement of the cruciate ligaments. Local recurrent disease was defined as histological proven recurrent disease.

Descriptive statistics were used to summarize the data. No further analyses were performed because of the small number and diversity of patients.

# Results

Of the 141 identified TGCT patients, 12 patients received additional cryosurgery. In the 129 patients without additional cryosurgery, 82 had diffuse disease. Fourteen of these patients had no treatment at our tertiary center. In 68 patients treated at our center the knee (n=59), hip (n=3), ankle (n=5) and elbow (n=1) were affected. Three patients were lost to follow up. The mean time from first treatment to follow up was 10 (range 0.6-41) years.

## Indications for cryosurgery

In the 12 cryosurgical patients, five had primary disease and seven had prior treatments (1-3 previous treatments). The mean time from diagnose to cryosurgical treatment was 4.5 (range 0.5-6.3) years. In 10 out of 12 patients, the entire intra-articular space was affected with extension in surrounding structures, such as bone, ligaments, fat and muscle tissue. All were diffuse type TGCT. Seven of these patients had extra-articular disease. The cruciate ligaments of the knee were involved in 6 out of 8 patients. In 7 out of 12 patients (n=4 knees, n=2 hips, n=1 ankle) there was bone involvement. Bone involvement and extended disease were reported to be indications for additional cryosurgery to surgical synovectomy.

In one patient with localized disease of the elbow, we retrospectively did not find the considerations for additional cryosurgery. Probably the surgeon wanted to minimize the chance on recurrent disease in this location.

In patients with DTGCT of the knee (n=59), 19 patients had extra articular disease, 4 patients had bone involvement, 52 patients had intracondylar involvement and 55 had extended disease or a combination of two, three or all four of these features. All five ankles had extended disease with extra-articular involvement, and one of these patients also had bony involvement.

## Recurrences

The mean follow up after cryosurgery was 7.7 (range 5.5-14.9) years. Five patients with the diffuse subtype developed recurrent disease after cryosurgery, at a mean time of 2.8 (range 0.7-9.0) years. All recurrences were diagnosed on MRI, which was performed when clinical symptoms of any kind in or nearby the affected joint presented. Four were also histologically confirmed. None of these five patients had primary disease, they already had recurrent disease at the time of cryosurgical therapy. One patient with recurrent disease received EBRT following initial cryosurgery. Another patient received a total hip arthroplasty (THA) during the same surgical procedure.

**Table 1** Demographics, previous recurrences and detailed description of treatments received before of in combination with additional cryosurgery.

| ID | Sex | Age (yrs) | Localized/ Diffuse | Previous recurrences | Follow-up before cryosurgery (yrs) | All treatments received | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1st | 2nd | 3rd | 4th |
| Knee | | | | | | | | | |
| 1 | F | 61 | Dt-GCT | 3 | 6.3 | SE | SE | tSE | tSE + cryo + EBRT |
| 2 | M | 58 | Dt-GCT | 2 | 9.7 | Yt | SE | tSE + cryo +EBRT | |
| 3 | F | 46 | Dt-GCT | 2 | 3.2 | SE | SE | SE + cryo | |
| 4 | M | 51 | Dt-GCT | 0 | 0.3 | tSE + cryo | | | |
| 5 | F | 25 | Dt-GCT | 1 | 3.0 | tSE | SE + cryo | | |
| 6 | F | 49 | Dt-GCT | 0 | 0.1 | SE + cryo | | | |
| 7 | M | 31 | Dt-GCT | 2 | 4.9 | tSE | SE | SE + cryo | |
| 8 | F | 31 | Dt-GCT | 0 | 0.0 | tSE + cryo | | | |
| Hip | | | | | | | | | |
| 9 | M | 44 | Dt-GCT | 2 | 0.5 | tSE | SE | SE+ THA + cryo | |
| 10 | F | 20 | Dt-GCT | 2 | 4.0 | SE | Yt | SE + THA+ cryo | |
| Ankle | | | | | | | | | |
| 11 | M | 34 | Dt-GCT | 0 | 0.0 | SE + cryo | | | |
| Elbow | | | | | | | | | |
| 12 | F | 21 | Lt-GCT | 0 | 0.7 | SE + cryo | | | |

F: female, M: male, SE: surgical synovectomy, tSE: two stage synovectomy (anterior and posterior compartment of the knee in two separate procedures), Yt: Yttrium radiosynovectomy, EBRT: External beam radiation therapy, Cryo: cryosurgery, Follow up before cryosurgery: the time from diagnose until the use of cryosurgery in years. THA: total hip arthroplasty

Three out of five patients with recurrent disease after cryosurgery developed a second or even third recurrence. Treatments following these recurrences are listed in table 2.

All four recurrences in patients with TGCT of the knee occurred within 2 years (9-22 months) after treatment. These patients had extended disease with involvement of the cruciate ligaments. In two patients with recurrent disease there was extra-articular disease and in one there was bone involvement. In the four knee patients without recurrences (of whom three were primary treated and one was treated with additional EBRT following cryosurgery), three had extended disease with bone involvement.

In the two patients with TGCT of the hip, one recurrence occurred nine years after cryosurgery. It was the third recurrence since onset of disease. At the time of cryosurgery, the acetabulum was affected by TGCT. Both patients also received a total hip arthroplasty for joint destruction by extended disease combined with secondary osteoarthritis. In both ankle and elbow, no recurrences were seen.
In patients with diffuse type disease whom did not receive additional cryosurgery 30 (44%) had recurrent disease. The mean time to first recurrence was 4.7 (range 0.7-27) years. All referred knee patients (n=26) had recurrent disease. Nine (34.6%) of these patients developed another recurrence after treatment at our center in 1.7 (range 0.7-4.4) years. In primary treated knee patients 16 (55%) had recurrent disease in 6.4 (range 1-27) years.



Twenty seven patients (40%) had extra-articular disease, 6 (9%) had bone involvement, 52 (77%) had involvement of the cruciate ligaments and in 64 (94%) patients there was extended disease or a combination of two, three or all four of these features. For example, in the 27 patients with extra-articular disease 6 had bone involvement, 18 had affected cruciate ligaments and all 27 had extended disease. Eighteen of these patients had recurrent disease in 7 (0.8-17) years follow up. The time to first recurrence was 1.9 (0.7-4.1) years. And 11 recurrences appeared after treatment at our center. All 6 patients with bone involvement had extra-articular disease and extended disease, including 4 patients with affected cruciate ligaments. Five of these patients had recurrent disease in 11 (2-17) years follow up. The time to first recurrence was 1.8 (1.2-3.2) years. Three recurrences appeared after treatment at our center.

Of five patients with TGCT in the ankle 4 had recurrent disease, two of which were primary treated patients. The mean time until first recurrence was 2.7 (1.2-4.1) years.

**Table 2** Indications, treatment details, follow up, recurrences with their treatments and complications of patients who received additional cryosurgery.

| Location | Indications for treatment | | | | Follow-up (FU) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient ID | Large expansion | Extra-articular disease | Bone involvement | Cruciate ligaments | Total FU (years) | Recurrence | Time until recurrence (years) | Treatment of recurrence 1e | 2e | 3e | Complications |
| Knee | | | | | | | | | | | |
| 1 | X | X | | X | 7.1 | Yes | 1.19 | TKA | | | |
| 2 | X | X | X | X | 9.4 | no | | | | | |
| 3 | X | | | X | 5.8 | yes | 1.85 | SE | Imatinib | | |
| 4 | X | X | X | | 5.8 | no | | | | | |
| 5 | X | | | X | 3.9 | yes | 0.73 | SE | SE+ EBRT | none | |
| 6 | | | | X | 8.3 | no | | | | | |
| 7 | X | X | X | X | 6.1 | yes | 1.47 | EBRT | Nilotinib | | Infection |
| 8 | X | | X | X | 7.6 | no | | | | | |
| Hip | | | | | | | | | | | |
| 9 | X | X | X | | 10.7 | yes | 9.03 | SE + cryo | | | Hip dislocation |
| 10 | X | X | X | | 14.9 | no | | | | | |
| Ankle | | | | | | | | | | | |
| 11 | X | X | X | | 5.5 | no | | | | | |
| Elbow | | | | | | | | | | | |
| 12 | | | | | 7.5 | no | | | | | |

Follow up: from cryosurgery until last patient contact, SE: surgical synovectomy, tSE: two stage synovectomy (anterior and posterior compartment of the knee in two separate procedures), EBRT: External beam radiation therapy, Cryo: cryosurgery, TKA: Total Knee Arthroplasty

### Complications

Two complications were reported in the cryosurgical group (table 2): A hip dislocation direct after arthroplasty, which was closed reduced. And a deep infection of the knee, three months after surgery, which was treated with surgical debridement and antibiotics.

## Discussion

TGCT is difficult to cure; in particular, the diffuse subtype frequently recurs. The treatment of first choice is surgical resection of all affected tissue. However, with extended and/ or extra-articular disease, bone involvement or disease at key locations inside the joint (ACL, PCL and collateral ligaments), resection of all affected tissue can be difficult to achieve. Various treatments (e.g. radiosynovectomy, EBRT, immune or targeted treatment) have been used, without the desired results.[76] We retrospectively evaluated the effect of additional cryosurgery in the treatment of TGCT.



We found indications of cryosurgery in addition to surgical resection for TGCT, were the presence of extended, extra-articular disease, affected bone or locations surgically difficult to get disease free, such as the cruciate ligaments. Furthermore, no recurrent disease was observed in patients primary treated with surgical synovectomy combined with cryosurgery. In patients known with recurrent disease additional cryosurgery was not effective.

Various indications were described for additional therapies in the treatment of TGCT.[76] The indications found for cryosurgery were similar to those considered for EBRT, except for patients with involvement of the neurovascular bundle. Cryosurgery is contraindicated in these patients. Effectiveness of radiosynovectomy in the treatment of TGCT is not proven and does not cover the extra-articular space.[41] Therefore, it is not indicated in patients with extended disease. Immunotherapy is not validated yet for the treatment of TGCT, however it has been applied in patients with extended disease.[20,135] For the use of targeted therapy in the treatment of TGCT, only small case studies and one retrospective cohort (29 patients) are published so far.[12,143,147,170] Due to the rapid relapse after discontinuation and severe side effects of targeted therapy, these treatments are only recommended for patients with surgical unresectable disease or multiple recurrences that produce clinical and functional impairment.[170] Other systemic treatments are individually available in trial-settings.[70]

Additional cryosurgery was not used after 2007 for different reasons: less extreme TGCT cases were presented the last years. The surgeon who often used cryosurgery for TGCT retired. Others preferred a more throughout resection of

affected tissue. There were definitely no adverse effects of cryosurgery that made us stop using it.

The number of recurrences in DTGCT with or without the use of cryosurgery were similar, respectively 45% after 2.8 years and 44% after 4.7 years. However, retrospectively it is difficult to determine if the patients in the cryosurgical group had worse disease compared to the other patients. In the cryosurgical group there was 90% extended disease, 64% extra-articular disease, 64% bone involvement and in 88% the cruciate ligaments were involved. The others had 94% extended disease, 40% extra-articular disease, 6% bone involvement and in 77% involvement of the cruciate ligaments.

In both groups there was a great difference in recurrences between referred patients versus primary treated patients. There were five (71%) recurrences after cryosurgery, in patients with prior treatments. Two out of seven patients with bone involvement had recurrent disease. None of the primary treated TGCT patients had recurrences after surgical synovectomy with cryosurgery. In the patients not treated with cryosurgery all referred knee patients showed recurrent disease of which 35% had recurrent disease after treatment at our center. There were 55% recurrences in the primary treated knee patients.

Mohler et al[49] described the use of cryosurgery in addition to surgical synovectomy in three patients (25-31 years of age) with TGCT of the knee. Two of these patients were diagnosed with recurrent disease. Cryosurgery was used during their third treatment. The other patient had primary disease. Two patients had extended disease. But, no details of bone involvement or involvement of the cruciate ligaments were described. No recurrent disease was found after 14-31 months follow up. However, TGCT recurrences are described up to 14 years later.[171]

Although cryosurgery is uncommon in the treatment of TGCT, it has been described for orthopedic oncologic diseases.[131] Reported complications as a result of cryosurgery are post-operative fractures (5-30%), infections (4%), transient nerve palsies and gas-embolisms (0.3%).[131] Also, damage to surrounding structures, such as the epiphysis and cartilage, have been described. In case of TGCT, the chance on fractures will be negligible though the intra-articular location. However, for this reason there might be an increased risk on damage to the joint cartilage. Furthermore, in TGCT the cartilage is often already damaged due to the disease itself, or to the multiple prior treatments. None of these complications were found in this study. However, one patient with recurrent disease after cryosurgery received a total knee arthroplasty for secondary osteoarthritis. Also, a post-operative dislocation of the hip and a deep infection of the knee three months after surgery occurred. These could be general complications after surgery; however, increased risk on infections have been described for cryosurgery.[131]

## Limitations

It is very difficult to produce a large volume study on treatment effects in a rare disease such as TGCT. For the subgroup of patients with extended disease, this is even more difficult. Therefore the study is limited by its retrospective character and the small number of patients. However, detailed information on received treatments was available and carefully described. Furthermore, some patients had other additional treatments next to cryosurgery, such as EBRT or arthroplasty what could have influenced our results. However, this was seen in both patient groups with and without recurrent disease. Despite these limitations, this article provides cautious insight for a possible role of cryosurgery in the treatment of TGCT. A prospective study with clear indications should follow to show if there is a role for cryosurgery in a subgroup of TGCT patients.

We conclude, cryosurgery may serve as an additional treatment for diffuse TCGT in selected cases. However, because of the small number of patients and the heterogeneous group we could not prove an advantage of additional cryosurgery over surgical resection only. Cryosurgery is a cheap, easy and relative harmless technique that should be considered for further evaluation in a prospective study with a sufficiently large number of patients, clear indications and a proper control group. If there is any effect it would be helpful, especially in patients with multiple TGCT recurrences.

# 8

# Long-term efficacy of imatinib mesylate in patients with advanced Tenosynovial Giant Cell Tumor- International, multicenter study

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## Abstract

Tenosynovial giant cell tumors (TGCT), are rare colony stimulating factor-1(CSF-1)-driven proliferative disorders affecting joints. Diffuse-type TGCT often causes significant morbidity due to local recurrences necessitating multiple surgeries. Imatinib mesylate (IM) blocks CSF-1 receptor. This study investigated the long term effects of IM in TGCT.

We conducted an international multi-institutional retrospective study to assess the activity of IM: data was collected anonymously from individual patients with locally advanced, recurrent or metastatic TGCT.

Sixty-two patients from 12 institutions across Europe, Australia and the United States were identified. Thirty-nine patients were female (63%), median age at treatment start was 45 (range 20-80) years, with a median time from diagnose to treatment of 3.5 (range 0-38,2) years. Median follow-up after treatment start was 52 (IQR 18-83) months. Four patients with metastatic TGCT progressed rapidly on IM and were excluded for further analyses. Seventeen of 58 evaluable patients achieved CR or PR. One- and five-year progression-free survival rates were 71% and 48%, respectively. Thirty-eight (66%) patients discontinued IM after a median of 7 (range 1-80) months. Reported adverse events in 45 (78%) patients were among other edema (48%) and fatigue (50%), mostly grade 1-2 (89%). Five patients experienced grade 3-4 toxicities.

This study confirms, with additional follow-up, the efficacy of IM in TGCT. In responding cases we confirmed prolonged IM activity on TGCT symptoms even after discontinuation, but with high rates of treatment interruption and additional treatments.

# Introduction

Tenosynovial giant-cell tumor (TGCT), historically known as pigmented villonodular synovitis (PVNS), is a rare, at times locally aggressive neoplasm affecting the joints or tendon sheaths in young adults. It is most common around large joints such as the knees, ankles and hips.[41,42] Known subtypes are localized and diffuse TGCT. The localized subtype comprises a single nodule and has a favorable course while the diffuse subtype involves the synovial lining as well as surrounding structures and is associated with a significant risk of recurrence (>50% depending on follow up times), despite being a benign neoplasm.[1,42,68] Metastatic forms have been described, but seem to occur very rarely.[172,173]

Surgical resection is the primary treatment for both subtypes. However, diffuse TGCT is difficult to remove completely and often requires a total synovectomy, or at time a joint replacement, or rarely even amputation.[41-43] In patients with extensive and/or recurrent TGCT, other available treatment modalities include radiation synovectomy[46], external beam radiation therapy[47], and cryosurgery.[174] Their therapeutic value has only been assessed in retrospective, in most cases single center series and their long term side effects and complications are poorly described.[76]

Recurrent TGCT is rarely lethal, but frequently becomes a debilitating chronic illness with substantial morbidity to the joints and quality of life impairment, caused by the disease itself and the multiple treatments.[20,42]

In TGCT, a neoplastic clone constitutes a subpopulation (2-16%)[12] of cells that overexpress colony-stimulating factor-1 (CSF-1). A t(1;2) translocation that links the *CSF1* gene on chromosome 1p13 to the *COL6A3* gene on chromosome 2q35 has been described and is believed to be responsible for the overproduction of CSF1 by neoplastic cells.[12,13] Inhibition of CSF1/CSF-1 receptor (CSF-1R) signaling has shown efficacy in the treatment of locally advanced and recurrent diffuse TGCT.[15,64,66]

Imatinib mesylate (IM) inhibits the CSF-1R kinase among other kinases.[64] We have previously reported on the efficacy of IM in TGCT. In the present study we provide long term follow-up on these initial patients and data on 33 additional consecutive patients.

# Methods

This retrospective study was conducted at 12 referral centers across Europe (9 institutions), the United States of America (2 institutions), and Australia (1 institution). The file of all patients with locally advanced, recurrent or metastatic TGCT, treated with IM were reviewed. Patients information were extracted from

individual patients' files at each institution by the local investigators and was provided in an anonymous form for final analyses. Histopathologic examination was performed at center of origin by pathologists with extensive experience in mesenchymal tumors. Response was measured using version 1.0 of Response Evaluation Criteria in Solid Tumors (RECIST). Data were described using percentages for qualitative variables and medians with ranges for continuous variables. Patients were not treated on a research protocol. They provided informed consent to treatment with a 'off-label' medical treatment, and treatment decision was left to the treating physician. This retrospective analysis was approved by the Ethics Committee in Lyon (Committee for the Protection of Individuals, Sud-Est IV, Lyon, France – L10-153 dated 9 December 2010).

Survival was plotted using the Kaplan-Meier method. Progression-free survival (PFS) was calculated from the date IM was started to the date of disease progression or death. The time to treatment failure (TTF) was calculated from the date IM was started to the date it was stopped because of toxicity, disease progression, or death, whichever occurred first. For patients with a surgical resection or other additional therapy after treatment with IM, PFS and TTF were censored at the time of surgery. Disease specific survival was calculated from the date IM was started to the date of death due to TGCT. Symptomatic response was defined as improvement of pain and/or joint function in patients who had symptoms at baseline. All statistical analyses were performed using R version 3.4.0 (R Foundation, Vienna, Austria).

# Results

## Patients

A total of 62 patients with histopathologically proven TGCT treated with imatinib were identified, their main characteristics are described in Table 1. Briefly, median age at diagnosis was 39 (IQR 31-53) years and 45 (IQR 36-56) years at start of treatment with IM, the majority of patients were female (N=39, 63%), and the knee (N=35, 56%) was the most commonly affected joint (Table 1). At start of IM treatment, three (5%) patients had biopsy proven metastatic disease, 15 (24%) locally advanced disease and 44 (71%) locally recurrent disease. Among patients with prior operations for TGCT (n=47), the median number of prior operations was 2 (range 1-9), and the time since the last operation was 23 (range 1-192) months. Median follow up of all patients was 52 (IQR 18-83) months.

## Treatment efficacy

Sixty-one patients received 400 mg and one patient received 600 mg IM daily. The 3 patients with metastatic disease at treatment start progressed rapidly on IM and

**Table 1** Descriptive of diffuse-type TGCT patients receiving imatinib mesylate treatment.

| | Patients N (%) |
|---|---|
| Total | 62 (100) |
| Median age at diagnosis (IQR), yrs. | **39 (31-53)** |
| Median time from diagnosis to start IM (IQR), yrs. | **3.5 (1-8)** |
| **Sex** | |
| Male | 23 (37) |
| Female | 39 (63) |
| **Tumor location** | |
| Knee | 35 (56) |
| Ankle | 11 (18) |
| Hip | 6 (10) |
| Foot | 4 (6) |
| Shoulder | 1 (2) |
| Elbow | 1 (2) |
| Head and Neck | 2 (3) |
| Wrist | 2 (3) |
| **Surgery before start IM** | |
| None | 15 (24) |
| 1-2 | 24 (39) |
| 3-4 | 13 (21) |
| >4 | 10 (16) |
| Median N of surgeries (range) | 2 (1-9) |
| Median time since last surgery (range), mo. | 23 (1-192) |
| **Disease status** | |
| **Locally advanced** | **20 (32)** |
| **Recurrence after surgery** | **39 (63)*** |
| **Metastatic disease** | 3 (5) |

Abbreviations: TGCT= Tenosynovial Giant Cell tumor, IM= imatinib mesylate, N= Number of patients, mo=months, yrs= years. *One of the locally recurrent patients progressed to metastatic disease.

were excluded from further analysis. One other patient with metastatic disease after multiple surgical treatments and IM, was excluded for further analyses too, leaving 58 patients for the rest of the analysis.

Median duration of IM treatment was 9 (IQR 5-27) months. At last follow-up, the majority of patients (n=38; 66%) had discontinued treatment. Seventy-seven

percent (95% CI 67-89), 41% (95% CI 29-57) and 36% (95% CI 25-52) of patients were still on IM after 6-, 12- and 24-months, respectively (figure 1). The treatment failure-rate was 82% (95% CI 71-95) after 12 months.

Response could not be assessed in 3 patients, two of which were lost to follow-up and one who discontinued early due to febrile neutropenia, leaving 55 patients with locally advanced or locally recurrent TGCT assessable for response. Seventeen patients (31%; 95% CI 19-43) had a RECIST-defined response, including 2 (3%) patients with a complete response. The median time to best response was 6 (range 1-23) months.

Forty of 51 patients (78%) reported symptom improvement (table 2), including 14 of 15 patients with radiological response (CR or PR). Among patients with radiological SD, 22 of 30 patients (73%), for whom data was available, had symptom improvement.

The 1-, 2- and 5-years overall PFS, metastatic patients (N=4) excluded, was 71% (95% CI 60-85), 60% (95% CI 48-75) and 48% (95% CI 36-65) respectively, (figure 2).

**Figure 1** Duration of imatinib mesylate treatment and progression free survival of this treatment in patients with locally advanced or recurrent diffuse-type TGCT.

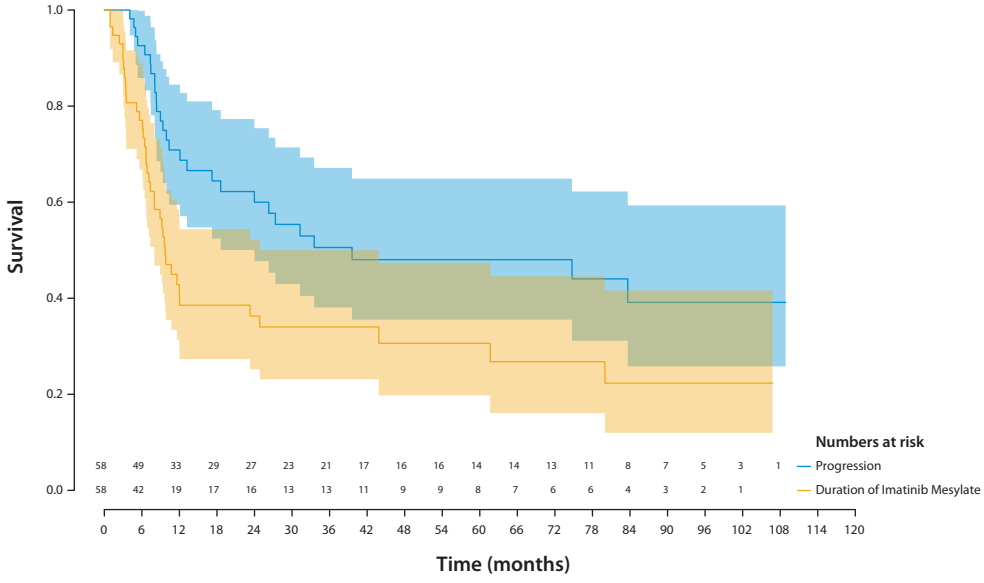


**Table 2** Summary of imatinib mesylate efficacy in patients with locally advanced or recurrent diffuse-type TGCT.

| Parameter | Patients N (%) |
|---|---|
| **RECIST best response*** | |
| Complete remission | 2 (4) |
| Partial response | 15 (27) |
| Stable disease | 36 (65) |
| Progressive disease | 2 (4) |
| Overall response rate | 17 (31) |
| Rate of disease control | 53 (96) |
| Symptomatic response | 40 (78)** |
| Median IM treatment duration (IQR), mo. | 9.3 (5-26) |
| Median PFS (IQR), mo. | 18 (8-55) |

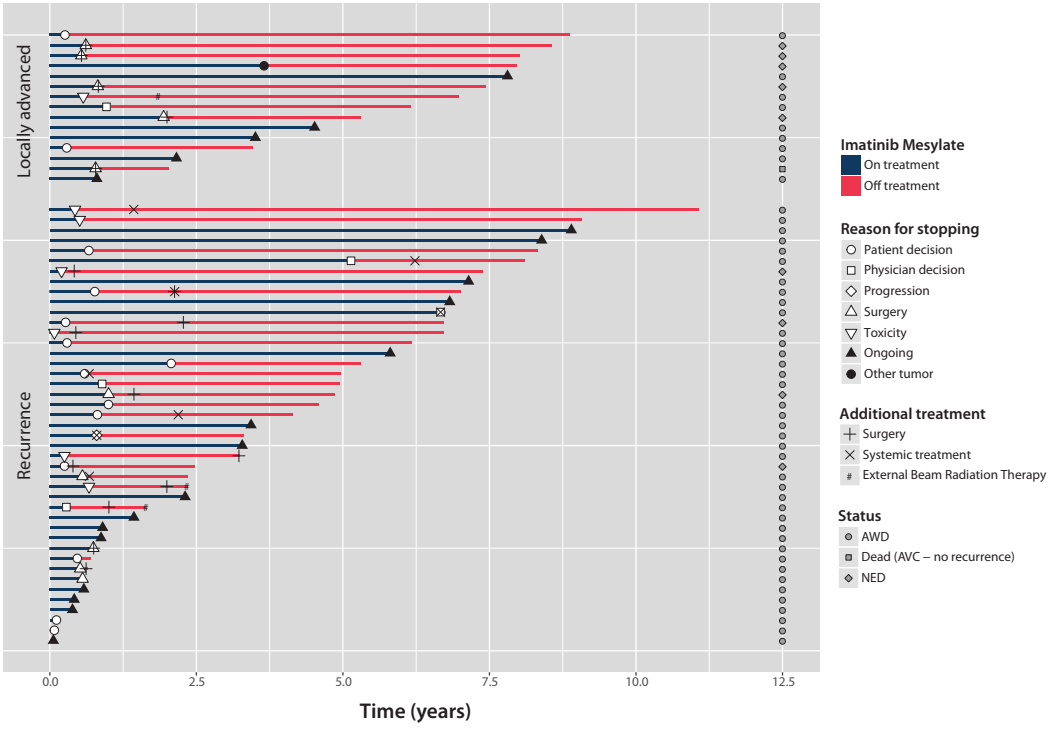
Abbreviations: TGCT= Tenosynovial Giant Cell tumour, IM= imatinib mesylate, N= Number of patients, mo=months, yrs= years, IQR= inter quartile range.
Overall response rate includes complete remission and partial response; Rate of disease control includes complete remission, partial response and stable disease; Symptomatic response was indicated as present or not (40/51=78%). Metastatic patients (n=4) were excluded.
*N=3 RECIST best response not available; **N=9 symptomatic response not available.



### Follow-up

Overall 38/58 patients (66%), metastatic patients (N=4) excluded, eventually discontinued IM after a median of 7.0 (range 1-80 months). the most common reason for treatment discontinuation was patient decision to stop (n=14, which possibly reflect low grade chronic toxicity), followed by planned surgery (n=10), toxicity (n=7), physician's decision (n=5) and progression (n=1). One patient discontinued IM because of the diagnosis of another tumor requiring therapy. Among the 27 patients who discontinued treatment for reasons other than surgery or progression, progression (either radiological progression or requirement for another line of therapy – i.e. surgery, other medical therapy or radiotherapy) eventually occurred 17 patients after a median of 12 (range 4-84) months, while 10 patients never progressed (nor required additional therapy) after a median follow-up to 78 (range 1-109) months, suggesting that IM was able to provide prolonged symptomatic relief at least in a proportion of patients.

**Figure 2** Response and follow up of imatinib mesylate in patients with locally advanced or recurrent diffuse-type TGCT.




NED= No evidence of disease, AWD= Alive with disease.

## Safety

Forty-five of 58 patients (78%), metastatic patients (N=4) excluded, reported at least one adverse event with IM. The most common adverse events were edema (N=28, 48%), fatigue (N=29, 50%), nausea (N=21, 34%) and skin rash/dermatitis (N=7, 12%), mostly grade 1-2 (89%). Additional grade 1-2 complaints were diarrhea, reflux, auditory hallucinations, conjunctivitis, sexual impairment, asthenia, alopecia, cramps and dyspnea. Five (11%) patients had grade 3-4 toxicities, including neutropenia, acute hepatitis, facial edema, skin toxicity and fatigue (table 3).

**Table 3** Main toxicities associated with imatinib mesylate and reasons for discontinuation, metastatic patients excluded.

| | Patients N (%) | |
|---|---|---|
| **Variable** | **All grades** | **Grade 3-4** |
| Edema/ fluid retention | 28 (48) | 1 (2) |
| Fatigue | 29 (50) | 1 (2) |
| Nausea | 20 (34) | |
| Skin rash/ dermatitis | 7 (12) | 2 (3) |
| Other* | 15 (26) | 3 (5) |
| **Treatment status** | | |
| Continued on IM | 20 (34) | |
| Stopped IM | 38 (66) | |
| **Reason for stopping** | | |
| Progression | 1 (2) | |
| Toxicity | 7 (12) | |
| Surgery | 10 (17) | |
| Patient choice | 14 (24) | |
| Physician decision | 5 (9) | |
| Other tumor | 1 (2) | |

IM= imatinib mesylate, N= Number of patients. Forty-five (78%) patients reported at least one adverse event with IM. *Other grade 1-2 complaints were diarrhea, reflux, auditory hallucinations, conjunctivitis, sexual impairment, asthenia, alopecia, cramps and dyspnea. Five (11%) patients had grade 3-4 toxicities, including neutropenia, acute hepatitis, auditory hallucinations.
Figure 1. Duration of imatinib mesylate treatment and progression free survival of this treatment in patients with locally advanced or recurrent diffuse-type TGCT.

## Discussion

To our knowledge, this retrospective study provides the largest case series, with long follow-up, of patients with locally advanced, recurrent or metastatic diffuse-type TGCT treated with IM. We confirmed that IM has activity in TGCT with an overall response rate of 31% in patients with locally advanced/recurrent TGCT. Interestingly all patients with metastatic TGCT progressed on IM, suggesting that metastatic TGCT is either a different disease or loses its dependency on the CSF1/CSF1R axis during malignant transformation. The main issue, is the drop-off rate, with more than half of the patients discontinuing therapy within a year of therapy (59%; 95% CI 29-57), in most cases for unclear reasons (patients decision, physician's decision) suggesting an unfavorable efficacy/toxicity balance. Eleven

percent of patients reported grade 3-4 toxicities, which is consistent with the rates reported with IM for adjuvant gastrointestinal stromal tumors (GIST) or chronic myeloid leukemia (CML).[175-178]

To date, surgical resection remains the treatment of choice for diffuse-type TGCT, but is associated with high recurrence rates and multiple additional surgeries.[76] It is challenging to balance between increased morbidity of multiples or invasive surgeries,[20,77] alternative therapeutic options, and daily symptoms of the tumor. A more aggressive resection or other multimodality treatments, such as external beam radiation therapy, radiosynovectomy and cryosurgery, may adversely affect joint function, quality of life and development of osteoarthrosis, which, given the young age group, are relevant factors.[38,42] This would justify a less invasive approach, using systemic therapy, provided those are associated with tumor shrinkage and, most importantly, symptomatic improvements.[16]

In the present study, age, localization and gender distribution were consistent with the literature.[18,38,174] The extent of disease in our patient group is emphasized by an disease specific survival of 90% including four metastatic patients and 49% of patients had three or more surgeries before start IM. Similar to previous case-series, we calculated a 1- and 5-years PFS of 71% and 48%, metastatic patients excluded, respectively.[18,38,174] Because of heterogeneity of patients and a variety of treatments, it is debatable to compare these numbers.

The overall response rate appears higher compared to nilotinib (6% (95% CI unknown), a different tyrosine kinase inhibitor, with similar potency against CSF1R.[179] Our overall response rate (31% (95% CI 19-43, metastatic patients (N=4) excluded) was consistent with our previous report on the short term results of IM (19% (95% CI 4-34) with similar disease control rate (96% versus 93%).[64] In the present study, 38 (66%) patients discontinued IM; 14 (37%) without subsequent treatment, of which ten patients had stable disease at final follow up. Thirteen (62%) patients eventually progressed, after discontinuing IM for toxicity or non-specific medical reason (N=21, 55%). Both stable and progressive patients can be a result of discontinuing IM treatment or the natural course of disease.

Newer, more specific inhibitors of CSF1R, currently only available in trial-setting such as emactuzumab (RG7155)[61], pexidartinib (PLX3397),[66] and cabiralizumab[62] (FPA008, Five-Prime), have shown promising clinical activity on similar groups of diffuse TGCT patients in prospective clinical studies with more formal criteria and timelines for response assessment than this retrospective series. Emactuzumab (N=29)[15] had an overall response rate of 86% (two patients with a complete response) and a rate of disease control of 96%, including a significant functional and symptomatic improvement (median follow up 12 months). Pexidartinib showed (N=23)[66] an overall response rate of 52% (all patients had a partial response) and a rate of disease control of 83%. Responses were

associated with an improved joint function (median duration of response exceeded eight months). The preliminary results with cabiralizumab (N=22) are consistent, with radiographic response and improvement in pain and function in five out of 11 patients.[62] However, long term efficacy data have not yet been reported with these newer agents.

Virtually all patients treated with IM for either CML or GISTs, experience[148] at least one mild or moderate adverse effect (grade 1-2). Toxicities of IM are determined by the disease stage and the doses used, advanced disease and higher doses result in more frequent and severe toxicities. Most side effects occur early in the course of treatment and tend to decrease in frequency and intensity in time.[148] We consider a 10-15% rate of grade 3-4 toxicities in a generally benign but locally aggressive disease, such as diffuse TGCT, too high. Only 22% of patients did not experience any side effects.

Although target anti-cancer therapies are described as 'well tolerated', the perception of tolerability may vary in the context of a, most often, benign condition. Understanding, monitoring and managing the side effects will be important to optimize systemic therapy for patients with TGCT.

Discontinuation of treatment due to toxicities was seen for IM (this series), emactuzumab[66] and pexidartinib[15] in 12%, 20% and 9% patients, respectively. TGCT patients might be less willing to cope with adverse event-related and study-related procedures. Here, we report prolonged clinical benefit and symptomatic relief, even after discontinuation of treatment. A similarly persistent effect was observed was also observed with monoclonal antibodies and more specific CSF1R tyrosine kinase inhibitors this.[16] This suggest that intermittent treatment administration may be an option to improve long term tolerability.

The place of systemic treatment in a benign, locally aggressive disease, such as TGCT, and how to optimally deliver this treatment, remains unclear. More specifically, the role of CSF1R inhibitors in the peri-operative setting still needs to be explored: the number of patients who underwent operation after IM in our series is too low to draw any conclusions. Despite limitations related to its retrospective nature, this study adds to the knowledge of targeting the CSF-1/CSF-1R pathway in patients with TGCT. An optimal treatment strategy should be developed for the patient group that benefits most from systemic therapy. The combination of a short period of treatment and the durable effect after discontinuation, should be pursued. It is challenging to maintain compliance for years, especially with, even "minor", toxicities, in the context of a non-life-threatening disease.

A limitation of all, including this, clinical TGCT studies is the lack of a control group and the absence of specific and validated patient-reported outcome measures to document treatment-induced symptomatic, functional and economic (back to

work) improvement.[15] Quality of life and functional forms should be implemented. These measures are critical endpoints in demonstrating clinical relevance and impact of treatments for benign diseases in which death is not a relevant outcome variable.[72] Clinical benefit necessitates objective measures to correlate with tumor reduction.

## Conclusion

Identification of a biologic aggressive subgroup of diffuse TGCT, at risk of increased surgical morbidity or recurrent disease, should aid to decide which patients benefit most of systemic treatments. With the advent of more potent CSF-1R inhibitors, such as emactuzumab, pexidartinib and cabiralizumab, the role of IM in extensive TGCT might weaken, but may be balanced by the favorable safety profile of IM. Availability of these new compounds, both in terms of registration and reimbursement, will ultimately define the prescribed drug in daily practice.

8

# 9

# Treatments of tenosynovial Giant Cell Tumors of the Temporomandibular joint: Report of three cases and a review of literature

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## Abstract

Tenosynovial giant cell tumours (TGCTs) are benign lesions affecting synovial joints. The classified subtypes are localized and diffuse. They seldom occur in the temporomandibular joint (TMJ). The aim of this study is to report on three new cases and to review the literature.

One patient had surgical debulking with adjuvant external beam radiation therapy (EBRT). After 1 year of follow-up, no evidence of disease was presented. The second patient was misdiagnosed and treated with denosumab. Debulking with adjuvant EBRT followed. Ten months postoperatively, no disease progression was seen. The third patient received systemic nilotinib and remained stable for over 5 years.

The literature review included 106 cases of which 95 had diffuse subtype. Most patients, had surgical excision. Thirteen (14%) patients received adjuvant EBRT. Eleven (14%) recurrences were identified. After 1-, 5- and 10-years of follow-up, an overall progression-free survival (PFS) of 99% (95% confidence interval (CI) 0.96–1), 80% (95% CI 0.68–0.94), 67% (95% CI 0.51–0.90) was calculated, respectively. Treatments for diffuse-TGCT-TMJ should be individualized depending on age, severity of symptoms, extent of disease and progression, expected mutilation of surgical interference, and current systemic treatment options. In stable disease a 'wait and see'policy, is a viable option. Additional treatments should be reserved for symptomatic, irresectable tumours or residual disease after surgical treatment with persistent complaints.

# Introduction

Tenosynovial giant cell tumours (TGCTs), formerly known as pigmented villonodular synovitis (PVNS), are benign lesions that can affect any synovial joint.[1,2] It is most common in large weight-bearing joints such as the knee, hip and ankle.[18] However rare, it does occur in the temporomandibular joint (TMJ) where it is even less common compared to malignancies such as sarcomas or metastases.[73]

TGCTs can be classified into localized and diffuse subtypes, which differ in clinical features and behavior.[1] Since 1973[180], over 100 TGCT cases with TMJ involvement have been reported.[181,182] Patients initially present with an indolent course of a painless pre-auricular swelling, that may become symptomatic with limited mouth opening or trismus as the tumour increases in size.[183] The duration of symptoms prior to diagnosis is on average, 11.5 months. Age at presentation is most common in the late 30s to 40s.[184]

On magnetic resonance (MR) imaging, an enlarged mass extending away from the joint with hemosiderin deposition, is typical for TGCTs.[185] This hemosiderin deposition can be depicted as 'blooming' on gradient echo or prominent hypointens on T1- and T2-weighted sequences.

Computed tomography (CT) can reveal areas of lytic bone erosion and sclerosis. Furthermore, it clearly defines the extent of the tumour, which is the focal areas of hyperdensity within the soft-tissue mass.

Both types of TGCTs are microscopically identical with a heterogeneous accumulation of both, neoplastic and non-neoplastic cells. The neoplastic cells overexpress colony stimulating factor 1 (CSF1) as a result of a translocation fusing CSF1 (at 1p11-13) to COL6A3 (at 2q35) that probably attracts the secondary non-neoplastic population of mainly histiocytes. This reactive component is known as the 'paracrine landscape effect'.[12,13]



Most reports of TMJ involvement describe the diffuse form, which can be locally aggressive with bone destruction and invasion of contiguous structures. In large joints, high recurrence rates over 50% are shown, depending on time followed.[42] In contrast, for TMJ recurrence rates of 15% with at least 1 year of follow-up were reported. However, in a limited cohort of seven cases, the rate of recurrence at 5 years was 29%.[182]

Management of TGCTs entails a complete synovectomy to remove all pathologic tissue. When complete removal is considered mutilating, additional treatments might be an alternative; external beam radiation therapy (EBRT), radiation synovectomy, cryosurgery, total joint arthroplasty and immune or targeted therapy. However, the effect of these treatments is unknown, caused by rarity of the disease and heterogeneity of the patients.[76]

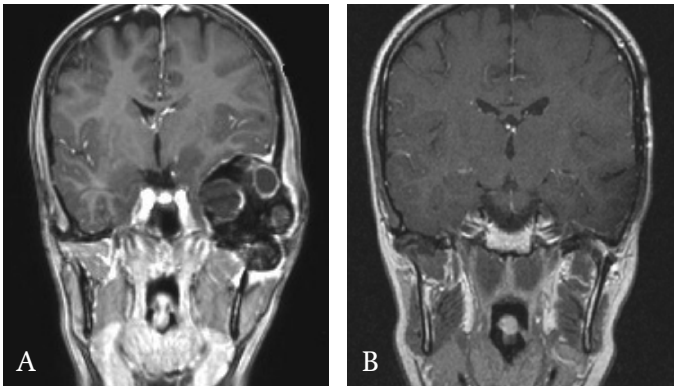
The aim of this study is to report on our experience of three TGCT-TMJ cases and review the relevant literature.

## Case reports

### Patient 1

A 20-year-old female patient had a progressive, pre-auricular, painful swelling and hearing loss, on the left side. She had complaints of headaches and nausea. Examination confirmed a painful pre-auricular solid-elastic, partially fluctuating swelling of 5 cm in diameter. On computed tomography (CT) and MR imaging (figure 1A), a large solid multilobular mass in the infratemporal fossa was detected with extension into the temporal bone showing destructive and lytic growth. The solid components were remarkably low in signal intensity on T1- and T2-weighted MR images, without bone matrix. An increased pressure on the temporal lobe was seen. No malignant characteristics were shown.

**Figure 1** MR images of a 20-year-old female with TGCT-TMJ on the left (patient 1).




(**A**) Preoperative MR images demonstrating a large solid multilobular mass in the infratemporal fossa with extension into the left temporal bone. An increased pressure on the temporal lobe was seen. No malignant characteristics were shown. (**B**) MR images 1 year after surgical TGCT-TMJ resection. There is minimal residual coloring around the TMJ, indicating scar tissue or reactive, without visible hemosiderine deposits.

A CT wired biopsy was performed from the solid osseous expansile temporal part of the tumour. It showed a benign mesenchymal lesion with giant cells. Differential diagnostic, a chondroblastoma with secondary aneurysmal bone cyst, or a diffuse type of TGCT were considered.

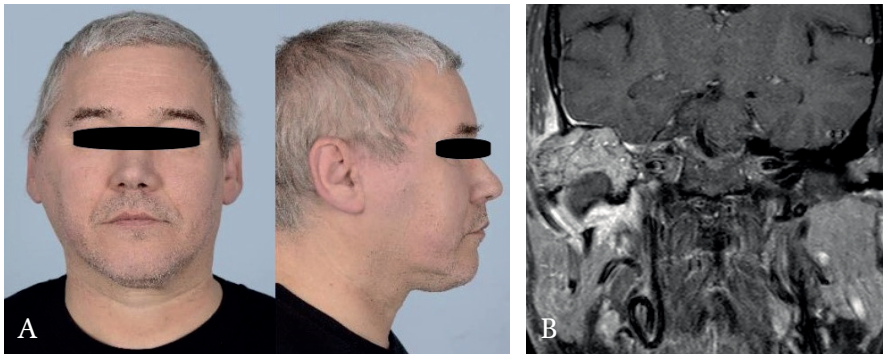
Three months after initial visit, the lesion extending from the TMJ involving the skull base and intracranial extension (extradural), was surgically removed. The tumour showed a multilobular yellow, rust-brown aspect with pigmentation. The adjacent dura remained intact. The skull base, the lateral os zygomaticus and the medial part of the temporal bone were eroded. A titanium mesh was implanted in the temporal bone defect. The musculus temporalis was positioned in the TMJ.

Because of the adjacent internal carotid artery, residual tumour and visible pigmentation remained. Definitive pathology report confirmed an irradical resection of a diffuse type of TGCT. The patient received adjuvant external beam radiationtherapy (11 weeks after surgery a total dose of 45 Gy in 1.8-Gy fractions), considering the irradical resection, in combination with the high risk of damage to vital structures. Attributed to the EBRT, the patient had transient complaints of fatigue, an itchy scalp, and local temporal hair loss. After 1 year of follow-up there was no evidence of progressive disease (figure 1B).

### Patient 2

A 54-year-old male had a progressive pre-auricular swelling and hearing loss on the right side, since 3 years. Examination showed trismus. The solid-elastic pre-auricular swelling with a diameter of 5 cm was attached to the bony layer (figure 2A).

**Figure 2** Preoperative clinical photo of a 54-year-old male with TGCT-TMJ on the right side (patient 2).




(**A**) A progressive pre-auricular swelling since 3 years. The solid-elastic pre-auricular swelling with a diameter of 5 cm was attached to the bony layer. (**B**) Preoperative contrast enhanced T1-weighted MR images show an extensive lesion in the TMJ with involvement of the temporal bone, an intact mandibular condyle and intracranial expansion including invasion of the temporal lobe. Mastoid breakthrough with destruction of the tegmen tympani, obstruction of the Eustachian tube and post-obstructive oto-inflammatory changes are presented.

CT and MR imaging (Figure 2B) showed an extensive lesion in the TMJ with involvement of the temporal bone, an intact mandibular condyle and intracranial expansion including invasion of the temporal lobe. Mastoid breakthrough with destruction of the tegmen tympani, obstruction of the Eustachian tube and post-obstructive oto-inflammatory changes were presented. Initially, TGCT was considered. However, open biopsies showed a giant cell lesion of bone histopathology suggesting a giant cell granuloma of bone (figure 3).

Denosumab[186], a RANKL (receptor activator of nuclear factor kappa-B ligand) inhibitor that inhibits formation and function of osteoclasts, was started for giant cell granuloma of bone (not for the final diagnosis: TGCT). After half a year there was increased bone formation and pain symptoms disappeared. Calcium and vitamin D3 were started to prevent a hypocalcemia.

After 15 months of stable disease, additional biopsies were taken to evaluate the effect of Denosumab[186]. Histopathologic examination showed vital giant cell lesion with fibrosis and necrosis. After 18 months of Denosumab treatment, the pre-auricular swelling increased concomitant with a persisting trismus. Operative debulking was performed. Trepanation and excision of the arcus zygomaticus were essential and macroscopic residual disease remained.

Histopathologic evaluation confirmed diffuse type TGCT. Additional postoperative EBRT (25 × 1.8 Gy) was necessary according to the tight resection margins. Denosumab treatment, given for a false diagnosis, was stopped.

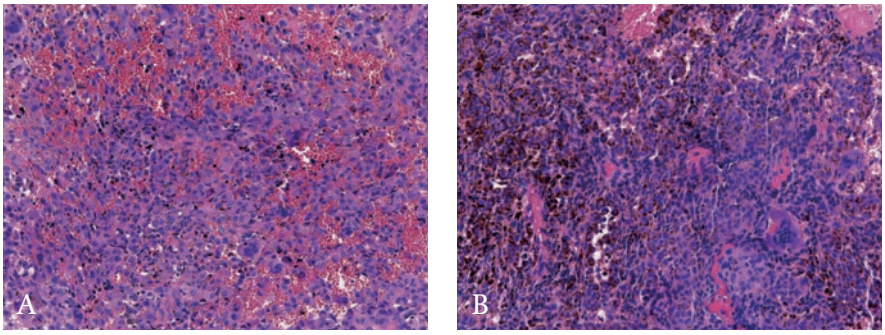
Besides temporary dryness of his right eye and mild erythema of the skin following EBRT, no other complaints were presented. Currently, 10months post-operatively, auditory perception on the right side is absent. The patient describes a decreasing pre-auricular painless swelling. His mouth opening is within normal ranges (38 mm).

**Patient 3**

A 27-year-old female presented with a painful TMJ on the left side and a decreased mouth opening, since 4 years. At maximum mouth opening slight deviation to the left was observed. Palpation of the ipsilateral TMJ was painful.

CT and MR imaging showed a space occupying intra-articular lesion on the TMJ with a diameter of 3.1 cm. Tumour involvement of the parafaryngeal space and both pterygoid muscles was presented. Laterally, the lesion affected the masseter muscle, the dorsal part of the zygomatic arch and the temporalis muscle. Medially, the tumour reached the oval foramen, which itself was not involved. Imaging and clinical presentation presumed either synovial chondromatosis or TGCT. Histopathologic examination, from a CT-guided cytological biopsy, confirmed TGCT diagnosis.

**Figure 3** Hematoxylin and eosin stain on tumour specimen demonstrating TGCT-TMJ (patient 2).




(**A**) Hematoxylin and eosin stained slides show sheets of monomorphic mononuclear cells of small or intermediate size with round to oval nuclei. Scattered around are multinucleated osteoclast-like giant cells. Focally, deposition of iron is presented (brown colored), in a hemorrhagic background. (**B**) Including prominent iron deposition and focal bone formation in the intraosseous part.

A primary surgical resection was considered mutilating and nilotinib showed effects in some patients (overall response rate nilotinib (6% (95% CI unknown)).[179] Therefore, the proposed treatment regime was 1 year nilotinib, a BCR-ABL tyrosine kinase inhibitor,[16] to reduce tumour size and to allow a more limited surgical resection. Side effects of nilotinib were hair loss, including eyebrows, and a rash. Multidisciplinary consultations discussed several treatment options: continuation of medical treatment, surgical resection or a 'wait and see' policy.

After 1 year of nilotinib treatment, surgery was reconsidered. Balancing between daily complaints and the mutilating aspect of surgery, a 'wait and see' policy was chosen. The patient was followed every 6 months, over 5 years. Consecutive MR imagines showed stable disease. Occasionally, the patient has complaints of a stabbing sensation, earache and limited mouth opening.



## Discussion

Presentation of TGCT-TMJ is extremely rare. It was first described by Lapayowker et al.[180] in 1973, followed by over 100 additional cases. There are two subtypes. The localized subtype, which involves only part of the synovium, showing a pedunculated well circumscribed nodule. And the diffuse subtype, that involves a large part or whole of the synovial membrane and often adjacent structures.[1] Distinction between subtypes is important, because diffuse lesions are more locally aggressive and recur more frequently.[42]

We reviewed 106 TGCT-TMJ cases (appendix 1); 103 selected patients of 70 retrieved articles from PubMed, including their reference lists and the current described three patients (appendix 1, table 1). Males (*n* = 62) and females (*n* = 43) were represented. There was an equal side distribution (left *n* = 44, right *n* = 43, NA *n* = 8). Ages ranged from 8 to 85 (median 45) years. Ninety-five patients had diffuse subtype, 10 localized subtype and in one case TGCT-subtype was not reported. All except two patients were treated with surgical resection. Thirteen (14%) patients received adjuvant EBRT for extended or residual disease. One patient had no treatment for advancing age and extended disease.

Patients present with a pre-auricular pain(less) mass, enlarging in time. Additional described symptoms as tinnitus, trismus, limited mouth opening, clicking and hearing loss depend on tumour extension and involvement of adjacent structures.[187,188]

The differential diagnosis of a pre-auricular swelling is extensive, including synovial cyst, ganglion, degenerative arthritis, synovial chondromatosis, mandibular osteoma, salivary gland tumours, chondrosarcoma, calcium pyrophosphate dehydrate deposition disease, rheumatoid arthritis, hemangioma, hemorrhage, osteoblastoma, aneurysmal bone cyst, brown tumour of hyperparathyroidism. Romanach et al.[188] described only 13% of TGCT-TMJ to be included in differential diagnosis prior to treatment. In 9% a malignant or metastatic tumour was proposed. Patient 2 was initially misdiagnosed with a giant cell granuloma of bone due to its bone-centered appearance. Nevertheless TGCT usually presents as a joint-centered lesion.[189] The following treatment (Denosumab) delayed diagnosis for 18months, in accordance with the average diagnostic delay described in literature (11.4 (±12) months).[184]

Clinical diagnosis of TGCTs is challenging. MR imaging in the right setting is pathognomic for the diagnosis, presenting a specific finding of low to intermediate signal in both T1- and T2-weighted images. The MR imaging low signal intensity areas of TGCT are best seen in T2-weighted images and are attributed to a paramagnetic effect produced by the reaction with high quantity hemosiderin. Hemosiderin causes the low signal intensity in MR imaging, known as the 'blooming effect'.[30,190] A CT scan shows extension of the lesion as well as bone destruction. When in doubt, diagnosis can be confirmed by a (open) biopsy.

Fine needle aspiration (FNA) cytology is often not sufficient to confirm TGCT diagnosis. This procedure frequently needs to be repeated several times, and diagnosis could remain inconclusive. However, it can be usually helpful in differentiating benign from malignant lesions. FNA shows mononuclear cells, multinucleated giant cells and histiocytes containing hemosiderin pigments.[191]

The treatment strategy for TGCTs should be influenced by the nature and clinical behavior of the lesion. Surgical removal of localized disease is relatively

easy. Still, in the knee recurrences up to 22% within 5 years were described.[42] To our knowledge, no recurrent disease has been reported for localized TGCT-TMJ.

Diffuse TGCT behaves naturally more aggressively compared to localized TGCT. Within the TMJ, 33% intra-cranial extension and/or middle ear involvement[182] and in 70.4% bone destruction is present.[184] The standard treatment for large joints is a partial or complete synovectomy, including parts of involved bones or surrounding tissue. TGCT-TMJ management includes mainly surgical excision, mostly with reconstructions that vary from no replacement, free costochondral or other bone grafts, metal condyle, total joint replacement to free vascular graft replacement options (most commonly the fibula).[192] Eisig et al.[193] recommended a wide excision. However, in TGCT-TMJ this is usually not feasible while adjacent to vital structures.

In patient 3, surgical resection was considered but refrained, given the risk of more treatment morbidity compared to the complaints of the benign disease itself. Reported complications after surgical resection were temporary or persistent mandibular deviation, tinnitus, facial paralysis, limited jaw movement, external auditory canal narrowing, hearing loss, liquor leakage and a scar.[194]

With extensive disease or disease in difficult attainable sites, adjuvant treatment(s) have been applied. However, none of these treatments proved to reduce recurrent rates.[76] Two of our current TMJ patients received postoperative radiotherapy for residual disease. In their relatively short follow-up, no recurrences/progression appeared. However, as described they experienced transient adverse effects. Joshi et al,[195] described grade 1/2 acute toxicities of radiation during treatment, including dysgeus, nausea, dermatitis and alopecia, which resolved. They conclude there could be a role for EBRT in extensive infiltrative tumours or positive margins. Chronic otitis media or hearing loss may occur following surgical resection with additional EBRT.



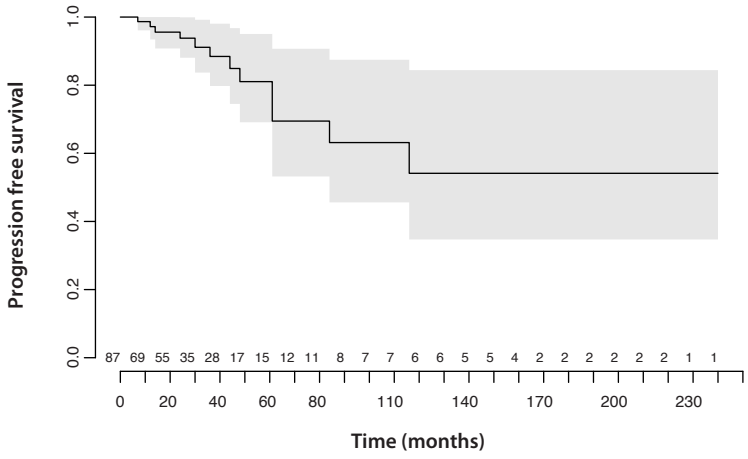
Patient 3 initially received targeted therapy (nilotinib) to reduce tumour size and to allow a more limited surgical resection. After 1 year of systemic treatment, the patient had stable disease which continued for over 5 years after discontinuation. She did not have surgery. To date, no systemic treatment is approved for TGCT, however inhibition of CSF1/CSF-1 receptor (CSF-1R) signalling has shown efficacy in the treatment of locally advanced and recurrent diffuse TGCT.[15,66] Larger cohorts, preferably randomized trials, are needed to evaluate the effect of systemic therapy targeting the CSF1/CSF1-receptor axis (imatinib, nilotinib, emactuzumab, and PLX3397 (pexidartinib)).[16]

Damodar et al.[133] reported earlier treatment inclines to have a better prognosis based on a literature review of 42 cases. However, two of our patients with a treatment delay of 3 and 4 years had stable disease for over 1-year, possibly according to systemic treatment. An expectative course for TGCT-TMJ can be considered in stable disease or relatively few clinical complaints, in contrast to

mutilating operations involving significant morbidity. The lesions can behave aggressively locally and show high recurrence rates, but malignant transformation or distant metastasis are only incidentally reported.[196]

According to our analyses of the literature, in diffuse TGCT-TMJ cases most patients had surgical resection (98%), some with adjuvant EBRT (14%) without accurate data regarding recurrence rates. It is difficult to predict recurrence rates because of the heterogeneity of the patient group and the lack of long-term follow-up information. We calculated an overall progression free survival (PFS) of 99% (95% CI 0.96–1), 80% (95% CI 0.68–0.94), 67% (95% CI 0.51–0.90) after 1, 5 and 10 years of follow-up, respectively, including 14% recurrences at a median follow-up of 24 (range 1–240) months (figure 4). The duration of follow-up in most cases is relatively short. Local recurrence rates would be expected to be higher with a longer follow-up. In the knee, recurrence rates over 50% are described with an overall PFS for diffuse TGCT of 68%, 32%, 25% and 16% after 1, 5, 10 and 15 years, respectively.[42]

**Figure 4** Kaplan–Meier survival curve showing progression-free survival of diffuse-type tenosynovial giant cell tumours in the temporomandibular joint.




Kaplan–Meier survival curve calculated from our own literature review. Uncertainty is shown by 95% confidence interval and a number-at-risk Table 1. Ninety-five diffuse-type cases were identified, 11 had recurrent disease at a mean time of 24 (range 1–240) months.

Tumour progression was managed by 6-monthly MR imagings. Carlson et al.[197] advised an MR imaging 3 months following surgery as a baseline, thereafter annually. However, 3 months after surgical treatment postoperative changes might still be present. We recommend an MR imaging, 6 months postoperatively, as a baseline scan to observe changes when symptoms arise. These symptoms might present after a long period of time, as TGCTs can recur after many asymptomatic years. No evidence exists that an annual MR imaging is contributory.[76] When there are no complaints, residual or recurrent disease, detected by scans is likely without treatment consequences.

**Table 1** Descriptive of patients with diffuse-type tenosynovial giant cell tumours in the temporomandibular joint of the current literature review.

| Number of patients (%) | 95 (90.5) |
|---|---|
| Gender n (%) | Female 43(41), male 62(59) |
| Median age, years (range) | 45 (8–85) |
| Surgical treatment n (%) | 93 (98) |
| Additional EBRT n (%) | 13 (14.3) |
| Follow-up, months (range) | Mean 42, median 24 (1–240) |

EBRT, external beam radiation therapy.



In conclusion, TGCT-TMJ is rare. It should be diagnosed by MR imaging scanning, if necessary with additional CT to evaluate the extent of disease. When in doubt, an open biopsy is conclusive for the diagnosis. The treatment for localized disease is an excision biopsy. For diffuse TGCTs several treatment options are available, which should be individualized by a multidisciplinary team (head and neck surgeon, (radiation-) oncologist, oncologic orthopaedic surgeon, neurosurgeon) depending on age, severity of symptoms, extent of disease and additional growth, expected mutilation of surgical interference, and the current systemic treatment options. In stable disease a 'wait-and-see' policy, with 6-monthly clinical follow-ups, is a viable option. With symptomatic complaints an MR imaging is indicated. Additional treatments, such as EBRT should be reserved for symptomatic irresectable tumours or where incomplete resection leaves residual disease with persistent complaints. Long-term clinical follow-up is recommended.

## Acknowledgements

We would like to thank the Dutch Bone Tumour Committee for reviewing these three cases, including advising on treatment options, and we highly appreciate the help of Gerjon Hannink in analysing the PFS.

**Table** Reported 106 cases of tenosynovial giant cell tumors of the temporomandibular joint.

| Author_ case number | Publication year | Age (years) | Sex | Subtype | Side | Follow up (months) | Recurrences | Time to recurrences (months) | EBRT | Surgery |
|---|---|---|---|---|---|---|---|---|---|---|
| Aimoni et al[198] | 2012 | 80 | M | DTGCT | Left | 18 | none | | none | yes |
| Allias-Montmayeur et al[199] | 1997 | 39 | F | LTGCT | NA | 7 | none | | none | yes |
| Aoyama et al[200] | 2004 | 33 | M | DTGCT | Right | 24 | none | | none | yes |
| Barnard[201] | 1975 | 37 | M | LTGCT | Left | 6 | none | | none | biopsy |
| Bredell et al[192] | 2015 | 34 | F | DTGCT | Right | 12 | none | | none | yes |
| Cai J et al[194] | 2011 | 59 | F | DTGCT | Left | 10 | none | | none | yes |
| Cai XY et al_1[202] | 2011 | 74 | F | DTGCT | Left | NA | NA | | none | yes |
| Cai XY et al_2[202,203] | 2009 | 21 | F | LTGCT | Left | 26 | none | | none | yes |
| Cai XY et al_3[202] | 2011 | 62 | F | DTGCT | Left | 44 | none | | none | yes |
| Cai XY et al_4[194] | 2011 | 25 | M | DTGCT | Right | 8 | none | | none | yes |
| Carlson_1[197] | 2016 | 43 | F | DTGCT | Right | 166 | none | | none | yes |
| Carlson_2[197] | 2016 | 40 | M | DTGCT | Right | 240 | none | | yes | yes |
| Carlson_3[197] | 2016 | 58 | M | DTGCT | Left | 226 | none | | yes | yes |
| Carlson_4[197] | 2016 | 60 | M | DTGCT | Left | 162 | none | | none | yes |
| Carlson_5[197] | 2016 | 57 | M | DTGCT | Left | 156 | none | | none | yes |
| Carlson_6[197] | 2016 | 31 | M | DTGCT | Right | 73 | none | | none | yes |
| Carlson_7[197] | 2016 | 42 | F | DTGCT | Right | 116 | yes | 16 | none | yes |
| Carlson_8[197] | 2016 | 49 | M | DTGCT | Left | 51 | none | | none | yes |
| Carlson_9[197] | 2016 | 79 | M | DTGCT | Right | 29 | none | | none | yes |
| Carlson_10[197] | 2016 | 54 | M | DTGCT | Right | 53 | none | | none | yes |
| Carlson_11[197] | 2016 | 39 | F | DTGCT | Right | 7 | none | | none | yes |
| Cascone et al[204] | 2005 | 38 | F | LTGCT | Left | 12 | none | | none | yes |
| Cascone et al[205] | 2008 | 78 | M | LTGCT | Right | 24 | none | | none | yes |
| Chen at al[206] | 2015 | 47 | F | DTGCT | Left | 40 | none | | none | yes |
| Chen et al[207] | 2008 | 56 | F | DTGCT | NA | 9 | none | | yes | yes |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Chow et al[187] | 1998 | 42 | F | DTGCT | Right | 24 | none | | none | yes |
| Church et al_1[208] | 2003 | 42 | M | DTGCT | Right | 36 | none | | none | yes |
| Church et al_2[208] | 2003 | 33 | M | DTGCT | Right | 24 | none | | none | yes |
| Damodar[133] | 2015 | 51 | M | DTGCT | Left | 6 | none | | none | yes |
| Dawiskiba et al[209] | 1989 | 32 | M | DTGCT | Right | NA | NA | | none | NA |
| Day et al[210] | 2008 | 38 | M | DTGCT | Left | 3 | none | | none | yes |
| Lapayowker et al_2[180], Dinerman and Meyers[211] | 1973,1977 | 58 | F | DTGCT | Left | 48 | none | | none | yes |
| Eisig et al[193] | 1992 | 50 | F | DTGCT | Right | 12 | none | | none | yes |
| Fang et all[212] | 2007 | 44 | M | DTGCT | Right | 20 | none | | yes | yes |
| Franchi et al[213] | 1994 | 59 | F | DTGCT | Left | 14 | none | | none | yes |
| Gallia et al[213], Curtin et al[215] | 1982, 1983 | 47 | F | DTGCT | Left | 24 | none | | none | yes |
| Gao et al[216] | 2016 | 45 | M | DTGCT | NA | NA | none | | none | yes |
| Geiger and Pesch[217] | 1980 | 50 | F | DTGCT | Left | 48 | none | | none | yes |
| Giannakopoulos[218] | 2013 | 48 | M | DTGCT | NA | 1 | none | | NA | NA |
| Gong et al[219] | 2010 | 34 | M | DTGCT | Right | 24 | none | | none | Yes |
| He et al[220] | 2012 | 34 | M | DTGCT | Right | 6 | none | | none | Yes |
| Heo et al[221] | 2003 | 45 | M | NA | NA | NA | NA | | NA | NA |
| Herman et al[184] | 2009 | 36 | M | DTGCT | Left | 132 | none | | none | yes |
| Hoch et al_1[222#] | 2011 | 8[#] | M | DTGCT | NA | 36 | none | | none | yes |
| Hoch et al _2[222] | 2011 | 67 | M | DTGCT | NA | 37 | Yes | 36 | none | yes |
| Hoch et al _3[222] | 2011 | NA | M | DTGCT | NA | 70 | none | | none | yes |
| Hoch et al _4[222] | 2011 | NA | F | DTGCT | NA | NA | none | | none | yes |
| Hoch et al _5[222] | 2011 | NA | F | DTGCT | NA | NA | none | | none | yes |
| Izzo et al[223] | 2005 | 67 | NA | LTGCT | Right | 1 | none | | none | yes |
| Joshi_1[195] | 2015 | 53 | M | DTGCT | Left | 48 | none | | yes | yes |
| Joshi_2[195] | 2015 | 30 | M | DTGCT | Left | 24 | none | | yes | yes |
| Il-Kyu Kim et al[183] | 2014 | 38 | M | DTGCT | Right | 120 | yes | 48 | NA | yes |
| K W Kim et al_1[190] | 2004 | 28 | F | DTGCT | Right | NA | NA | | NA | NA |
| K W Kim et al_2[190] | 2004 | 22 | M | DTGCT | Left | NA | NA | | NA | NA |

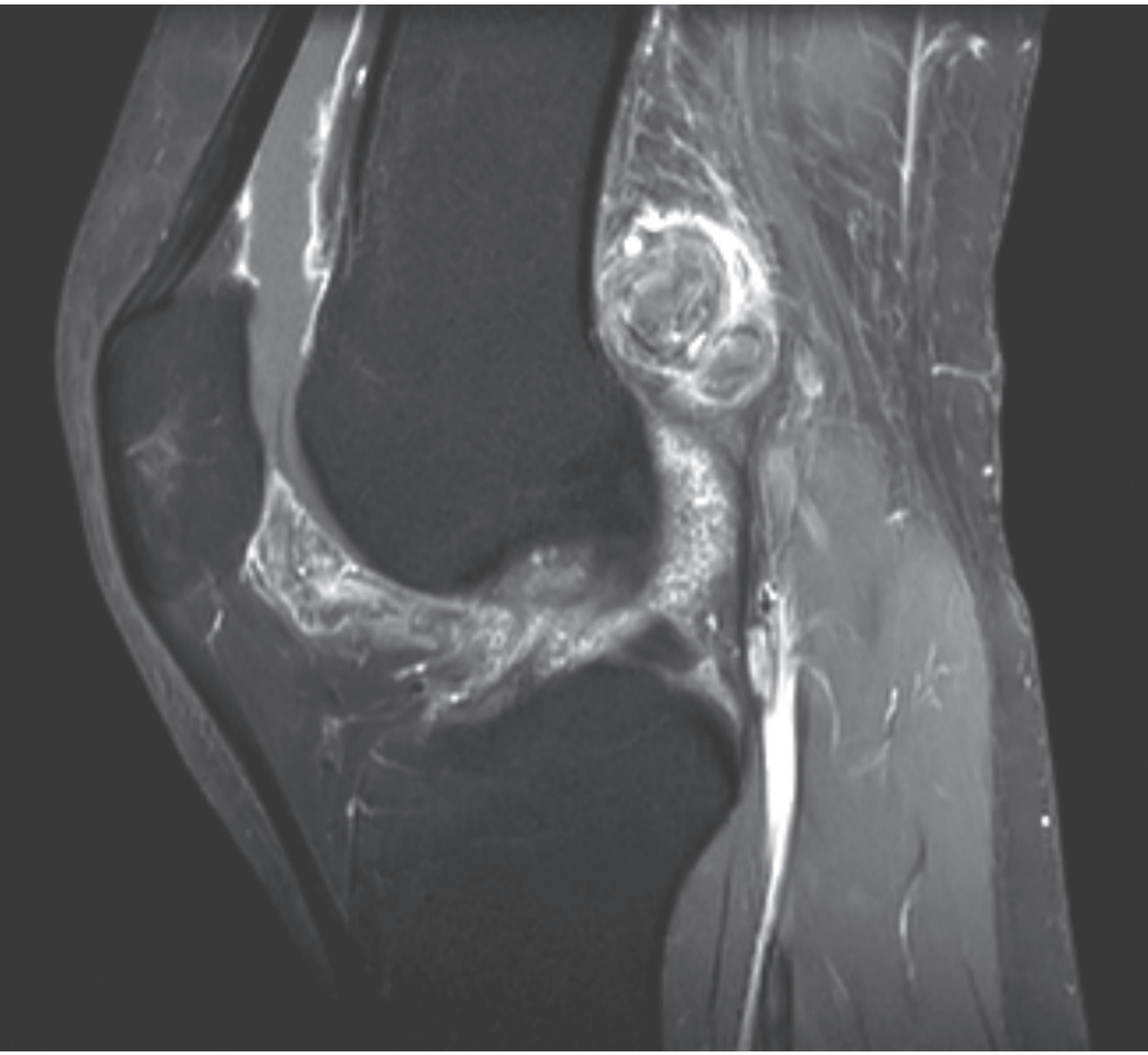
**Table** Continued.

| Author_ case number | Publication year | Age (years) | Sex | Subtype | Side | Follow up (months) | Recurrences | Time to recurrences (months) | EBRT | Surgery |
|---|---|---|---|---|---|---|---|---|---|---|
| K W Kim et al_3[190] | 2004 | 47 | M | DTGCT | Left | NA | NA | | NA | NA |
| K W Kim et al_4[190] | 2004 | 58 | F | DTGCT | Right | NA | NA | | NA | NA |
| Kisnisci et al[224] | 2001 | 45 | F | DTGCT | Left | 12 | none | | none | yes |
| Klenoff et al[225] | 2001 | 35 | M | DTGCT | Right | 36 | none | | none | yes |
| Kunz et al[226] | 2003 | 13 | M | DTGCT | Right | 24 | NA | | none | yes |
| Lapayowker et al_1[180] | 1973 | 22 | M | DTGCT | Left | 99 | none | | none | yes |
| Le_1[227] | 2014 | 53 | F | DTGCT | Left | 48 | none | | NA | yes |
| Le_2[227] | 2014 | 38 | F | DTGCT | Left | 41 | none | | NA | yes |
| Le_3[227] | 2014 | 31 | M | DTGCT | Left | 41 | none | | NA | yes |
| Le_4[227] | 2014 | 49 | M | DTGCT | Left | 6 | none | | NA | yes |
| Le_5[227] | 2014 | 50 | F | DTGCT | Right | 24 | none | | NA | yes |
| Le_6[227] | 2014 | 34 | M | DTGCT | Right | 14 | yes | 14 | NA | yes |
| Le_7[227] | 2014 | 48 | M | DTGCT | Left | 7 | yes | 7 | NA | yes |
| Le_8[227] | 2014 | 56 | F | DTGCT | Right | 4 | none | | NA | yes |
| Lee et al[228] | 2000 | 59 | F | DTGCT | Right | 24 | none | | none | yes |
| Leiggener et al[229] | 2010 | 22 | M | DTGCT | Right | 36 | none | | none | yes |
| Liu et al[189] | 2012 | 56 | F | DTGCT | Left | 28 | none | | yes | yes |
| Lu et al[230] | 2011 | 42 | M | DTGCT | Left | 44 | yes | 44 | none | yes |
| Makek and Drommer[231] | 1978 | 55 | F | LTGCT | Right | 9 | none | | none | yes |
| Miyamoto et al[232] | 1977 | 34 | M | LTGCT | Right | 24 | none | | none | yes |
| Oda et al_1[233] | 2007 | 52 | M | DTGCT | Right | 11 | none | | none | yes |
| Oda et al_2[233] | 2007 | 67 | M | DTGCT | Left | 87 | none | | none | yes |
| Omura et al[234] | 1998 | 18 | M | DTGCT | Left | 24 | none | | none | yes |
| O'Sullivan et al[235], Bertoni et al[196] | 1984, 1997 | 61 | F | DTGCT | Left | 96 | yes | 18 | yes | yes |
| Pianosi et al[181] | 2016 | 85 | M | DTGCT | Left | 12 | none | | none | none |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Raibley[236] | 1977 | 62 | F | LTGCT | Left | 5 | none | | none | yes |
| Renaga–Rubinet al[237] | 1997 | 70 | F | DTGCT | Left | 36 | none | | none | yes |
| Rickert and Shapiro[238] | 1982 | 39 | F | DTGCT | Left | 3 | none | | none | yes |
| Romanach et al[188] | 2011 | 26 | M | DTGCT | Left | 18 | none | | yes | yes |
| Safaee_1[182] | 2015 | 55 | M | DTGCT | Left | 71 | yes | 61 | none | yes |
| Safaee_2[182] | 2015 | 26 | F | DTGCT | Right | 3 | none | | none | yes |
| Safaee_3[182] | 2015 | 58 | M | DTGCT | Left | 28 | none | | yes | yes |
| Safaee_4[182] | 2015 | 52 | M | DTGCT | Right | 6 | none | | yes | yes |
| Safaee_5[182] | 2015 | 35 | M | DTGCT | Left | 46 | none | | none | yes |
| Shapiro et al[191] | 2002 | 36 | M | DTGCT | Right | 84 | none | | none | yes |
| Shkoukani et al[239] | 2009 | 74 | F | DTGCT | Right | NA | none | | none | yes |
| Song et al[240] | 1999 | 57 | F | DTGCT | Right | NA | NA | | none | yes |
| Stojadinovic et al[241] | 1998 | 63 | M | DTGCT | Right | 20 | none | | none | yes |
| Bemporad et al[242], Stryjakowska_1[243] | 1999, 2005 | 37 | M | DTGCT | Right | 36 | none | | none | yes |
| Stryjakowska_2[241] | 2005 | 36 | F | DTGCT | Right | 27 | yes | 12 | none | yes |
| Syed et al[244] | 1993 | 10 | F | DTGCT | Left | 2 | none | | none | yes |
| Takagi and Ishikawa[245] | 1981 | 36 | M | DTGCT | Right | 193 | yes | 61 | none | yes |
| Tanaka et al[246] | 1997 | 47 | M | DTGCT | Right | 24 | none | | none | yes |
| Tel et al[247] | 2012 | 29 | M | DTGCT | Right | 60 | none | | none | yes |
| Tosun et al[248] | 2004 | 60 | M | DTGCT | Left | 84 | none | | none | yes |
| Verspoor et al _1* | 2017 | 20 | F | DTGCT | Left | 12 | none | | yes | yes |
| Verspoor et al _2* | 2017 | 54 | M | DTGCT | Right | 10 | none | | yes | yes |
| Verspoor et al _3* | 2017 | 27 | F | DTGCT | Left | 60 | none | | none | none |
| Wong et al[249] | 2012 | 51 | F | DTGCT | Left | 12 | none | | none | yes |
| Yoon et al[172] | 2011 | 29 | M | DTGCT | Right | 30 | yes | 30 | none | yes |
| Youssef et al[250] | 1996 | 41 | F | LTGCT | Left | 14 | none | | none | yes |
| Yu et al[251] | 1997 | 48 | M | DTGCT | Right | NA | NA | | none | yes |

NA= Not Available, M=Male, F= Female, DTGCT= Diffuse Tenosynovial Giant Cell Tumor, LTGCT= Localized Tenosynovial Giant Cell Tumor, EBRT= External Beam Radiation Therapy, *= Current article, #=Hoch et al[221] described an age range 36-70 (mean 49) years, 3 males an d 2 females, follow up range 8-67 (mean 29) months. All other articles described exact numbers.

# Outcome



# 10

# Long-term follow-up results of primary and recurrent pigmented villonodular synovitis

FGM Verspoor, AA Zee, G Hannink, IC van der Geest, RP Veth, HWB Schreuder.

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## Abstract

Adequate documentation of the outcome of treatment of pigmented villonodular synovitis (PVNS) is sparse. Available case series show relatively short follow-up times and often combine locations or subtypes to increase patient numbers. This article describes the long-term follow-up of a single institution's large consecutive series of PVNS.

Retrospectively, 107 PVNS patients were identified between 1985 and 2011 by searching pathology and radiology records. Treatment complications, recurrences and quality of life were evaluated. Most patients (85.2%) were primarily or secondarily treated at our institution.

Both subtypes, localized PVNS [29 (27%)] and diffuse PVNS [75 (70%)] were represented. The knee was affected in 88% of patients. Treatments received were surgery, external beam radiotherapy, radiosynovectomy, targeted therapy, immunotherapy or combinations of these. Forty-nine (46%) patients had prior treatment elsewhere. The mean follow-up from diagnosis until last contact was 7.0 years (range 0.3-27.4) for localized PVNS and 14.5 years (range 1.1-48.7) for diffuse PVNS. The 1- and 5-year recurrence-free survival rates for diffuse PVNS were 69% and 32%, respectively. Quality of life, estimated by 36-item Short Form Health Survey (SF-36) scores, were not significantly different between localized and diffuse PVNS. However, both patient groups scored lower than the general population norms on the general health component (59.2 and 56.3, respectively, $P < 0.05$).

Recurrence rates of PVNS increase with time. Long-term follow-up shows, particularly in diffuse PVNS, it is a continually recurring problem, and over time it becomes increasingly difficult to cure. The quality of life is decreased in patients with PVNS compared with the general population.

## Introduction

Pigmented villonodular synovitis (PVNS) is a rare, benign tumour originating from the synovial membrane. [2,4] The approximate annual incidence is 1.8 patients per million US inhabitants.[4] There is a predilection for weight-bearing extremities, with the knee joint being particularly affected.[31,252] PVNS is characterized by an aggressive clinical behaviour, with progressive destruction of affected joints.

Two main subtypes are identified based on clinical and radiological presentation.[8,30] The localized (L-PVNS) form is characterized by discrete nodular or pedunculated lesions. Clinically it simulates a mechanical derangement and L-PVNS rarely recurs (0-15%).[3,5,75,116,253] The diffuse (D-PVNS) form is most common and involves the intra- articular soft tissue lining and presents as a more chronic process. Reported recurrence rates after D-PVNS treatment range from 9% to 46%, depending on follow-up time.[4,19,36,39,41,51,52,54,55] PVNS may result in a long course of disease associated with multiple interventions leading to loss of joint function, early secondary osteoarthritis and treatment complications.[4,51,54,55]

Over the last 100 years, limited progress has been achieved in treatment strategies.[76] Generally PVNS is treated by surgical removal of all pathological tissue.[55] In cases of residual or recurrent disease, other treatment modalities have been tried, such as external beam radiation therapy[39,120], radiation synovectomy[55], cryosurgery[49], total joint arthroplasty[44,119] and immune[141] or targeted therapy[64,68].

Due to the small number of patients affected, no large prospective clinical trials on treatment results exist. All currently available evidence is based on retrospective case series. Outcome measures such as recurrence rates, recurrence-free survival (RFS) and joint function scores are often contaminated by combining subtypes, locations, treatments and both primary and recurrent disease to increase patient numbers, which leads to difficulties in interpretation and comparability of results.[4,44,50,75,119,120] To the best of our knowledge, there is no information available on quality of life (QoL), an important measure in a disease as destructive as PVNS. We performed a retrospective study on a relatively large number of patients with respect to recurrence rates, RFS, complications and QoL.



## Patients and methods

We retrospectively searched pathology and radiology patient databases on PVNS, nodular tenosynovitis, local tenosynovitis and giant cell tumour (GCT) of the tendon sheath. Between 1985 and 2011, a total of 184 patients were identified. After careful evaluation of the database records, 58% of patients were found to have PVNS. The 33% of GCT patients and 9% of patients that did not fit the

histological or MRI description of PVNS were excluded. Twenty-seven per cent of PVNS patients were classified as L-PVNS, 70% as D-PVNS and 3% as unknown. The demographics of the 104 L-PVNS and D-PVNS patients included in this study are provided in table 1. All cases were monoarticular.

Medical records were studied on clinical, pathological, radiological, treatment and follow-up information by two independent reviewers (F.G.M.V. and A.A.G.Z.). Any disagreements were resolved by consensus with a third reviewer (H.W.B.S.). QoL was evaluated by using the Dutch translation of a generic QoL instrument, the 36-item Short Form Health Survey (SF-36).[254]. The SF-36 is an instrument for measuring general health. It includes scales for physical functioning, social functioning, role physical functioning, role emotional functioning, mental health, vitality, bodily pain, general health and health change. All patients were contacted by telephone to take the SF-36 questionnaire. Sixty-two (57%) patients responded. The remaining patients could not be contacted because they had moved or changed telephone numbers. The study was approved by the institutional review board of the Radboud University Medical Center, Nijmegen (file number CMO 2012/555) and was carried out in line with the Declaration of Helsinki. Written informed consent was obtained from each patient

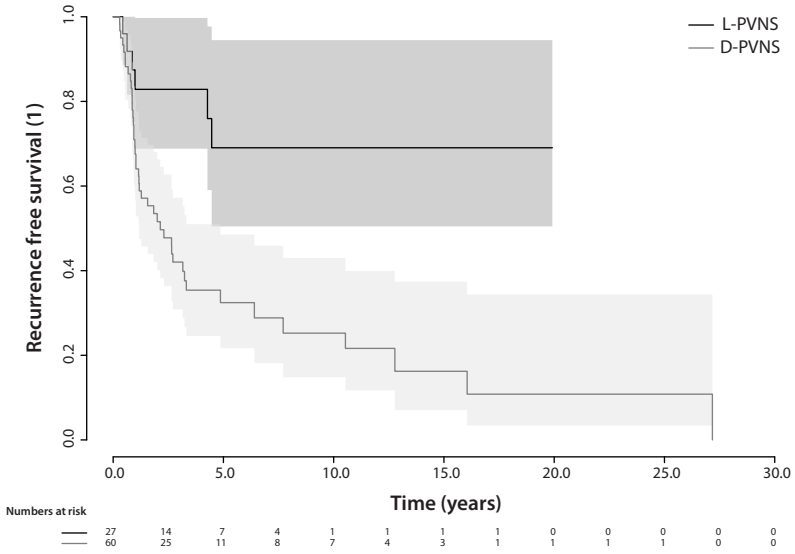
**Table 1** Demographics.

| | L-PVNS | D-PVNS |
|---|---|---|
| Patients, n (%) | 29 (100) | 75 (100) |
| Sex | | |
| Male, n (%) | 9 (31) | 36 (48) |
| Age at diagnosis, mean (S.D.), years | 39.7 (13.3) | 32.1 (10.1) |
| Females, n (%) | 20 (69) | 39 (52) |
| Age at diagnosis, mean (S.D.), years | 36.5 (14.4) | 35.7 (13.6) |
| Primary, n (%) | 23 (79) | 33 (44) |
| Referred, n (%) | 6 (21) | 42 (56) |
| Location, n (%) | | |
| Knee | 27 (93) | 64 (85) |
| Hip | 1 (3) | 5 (7) |
| Ankle | 0 | 6 (8) |
| Elbow | 1 (3) | 0 |
| Follow-up from diagnosis, mean (S.D.), years | 7.2 (7.0) | 13.9 (10.3) |
| Follow-up from index treatment, mean (S.D.), years | 6.6 (6.7) | 11.2 (9.8) |

Index treatment: first treatment in a tertiary centre; L-PVNS: localized pigmented villonodular synovitis; D-PVNS: diffuse pigmented villonodular synovitis.

Recurrences, treatment complications and current QoL were analysed according to PVNS subtype, location and primary and recurrent disease. Since the knee was affected in 88% of patients, analyses focused on this group. Recurrences are expressed as rates. The primary patient group received all treatments at our institution, while the referred patient group had their initial treatment(s) elsewhere and was treated at our institution for recurrent disease. The length of follow-up was defined as the period between the first pathology confirmation of diagnosis and the most recent patient contact. The time to recurrence was calculated as the time from the last treatment until histologically proven recurrent disease. Statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used for demographic data and patient characteristics. Between-group differences in SF-36 scores were compared using one-way analysis of variance followed by Bonferroni *post hoc* comparison tests. RFS analyses were performed using the Kaplan-Meier method and compared using log-rank tests. Survival estimates are presented as RFS (S.E.). Assumptions for individual tests were checked before the analyses were performed. For all data sets, differences were considered statistically significant at *P*-values <0.05.

**Figure 1** Kaplan-Meier curves showing recurrence-free survival for localized and diffuse pigmented villonodular synovitis.




Uncertainty is shown by 95% CI and a number-at-risk table below the graph. Recurrences were more frequent for diffuse pigmented villonodular synovitis. L-PVNS: localized pigmented villonodular synovitis; D-PVNS: diffuse pigmented villonodular synovitis

# Results

## Localized pigmented villonodular synovitis

The localized group contained 69% females [mean age 36.5 years (range 19.4-71.7)] and 31% males [mean age 39.7 years (range 17.1-53.3)]. The knee joint was affected in 93% of patients.

### Treatments and recurrences

Twenty-two affected knees were primary L-PVNS patients and five patients were referred. In 83% diagnosis was confirmed by MRI. In 34% diagnosis was preoperatively determined by biopsy. All patients were treated by open or arthroscopic surgical excision. In three of these patients, PVNS was an accidental finding during prosthetic surgery. Six patients needed additional surgical treatment, five for recurrent disease, two of which were first treated at our centre, two who received initial treatment elsewhere and one who received both treatments elsewhere. One patient was operated on four times due to residual pain and hydrops; however, recurrent disease was never demonstrated. Another patient initially received yttrium radioisotopic synoviorthesis, then recurrent disease developed and surgical excision was successfully applied. One patient who developed recurrent disease after surgical intervention had a successful yttrium radioisotopic synoviorthesis.

### Follow-up

The mean overall follow-up from diagnosis until last patient contact was 7.0 years (range 0.3-27.4). Of these knee patients, 15% of recurrences occurred within the first year and 22% within 5 years. The overall 1- and 5-year RFS was 83% and 69%, respectively (figure 1). For primary patients the RFS was 89% and 80%, respectively.

### Complications

Three patients had postoperative complications after surgical excision of L-PVNS tissue—two after initial treatment, one of which had a superficial wound infection successfully treated with antibiotics. The other patient had a deep infection that was treated by two operations and one manipulation under anaesthesia because of stiffness. Another patient suffered from a femoral nerve neuropathy after a second surgical excision, but recovered spontaneously.

### Quality of life

The SF-36 score was obtained for 70% of L-PVNS knee patients on average 6.1 years (range 1.2-19.9) after the first treatment. Table 2 shows the mean scores of all SF-36 scales. Compared with the general population[154], L-PVNS patients scored significantly lower on mental health ($P = 0.05$), vitality ($P= 0.02$) and general health ($P= 0.005$).

## Diffuse pigmented villonodular synovitis

The D-PVNS group contained 52% females [mean age 35.7 years (range 14.4-62.2)] and 48% males [mean age 32.1 years (range 16.7-52.9)]. The knee joint was most affected, in 85% of patients (table 1). In 25% of patients the diagnosis was obtained by biopsy, while in the remaining cases diagnosis was conclusive by MRI.

**Table 2** Outcome quality of life for pigmented villonodular synovitis knee patients compared with the general population at last follow-up.

| SF-36 subscale | L-PVNS, mean (SD) | D-PVNS, mean (SD) | General population, mean (SD) |
|---|---|---|---|
| Physical functioning | 72.4(27.0) | 68.2 (26.8)* | 81.9(23.2) |
| Social functioning | 82.2(27.7) | 86.8(25.6) | 86.9(20.5) |
| Role physical | 68.4(43.2) | 69.1(38.5) | 79.4(35.5) |
| Role emotional | 87.7(31.8) | 91.2(26.3) | 84.1(32.3) |
| Mental health | 67.6 (18.9)* | 70.1 (15.4)* | 76.8(18.4) |
| Vitality | 55.5 (19.4)* | 55.7 (20.4)* | 67.4(19.9) |
| Bodily pain | 68.7(34.7) | 74.0(26.7) | 79.5(25.6) |
| General health | 59.2 (18.0)* | 56.3 (18.6)* | 72.7(22.7) |
| Health change | 55.3(15.8) | 48.5(19.4) | 52.4(19.4) |

*Significant *P*-value <0.05 different compared with the general population. L-PVNS: localized pigmented villonodular synovitis; D-PVNS: diffuse pigmented villonodular synovitis. General population data reproduced from VanderZee KI *et al.*[153]

### Treatments and recurrences

Twenty-seven affected knees had primary lesions and 37 had recurrent disease after treatment(s) elsewhere. All primary D-PVNS patients, except for one, initially received surgical excision of PVNS tissue. Of these 27 primary D-PVNS patients, 6 had one recurrence and another 6 had two or more recurrences (table 3 and see supplementary Table S1, available at Rheumatology Online). Their mean follow-up from diagnosis was 13.0 years (range 1.1-48.7).

Of the 37 referred patients, 26 initially received surgical excision of PVNS tissue. Six patients initially received yttrium radioisotopic synoviorthesis. In two patients, it was not possible to retrieve information on initial treatment(s). Subsequent treatments and recurrences of all D-PVNS knee patients are described in table 3 (also see supplementary table S1, available at Rheumatology Online). Of two patients solely treated elsewhere, one patient was advised a complete synovectomy, but it remains unclear whether it was performed because this patient was lost to follow-up. In another patient, symptoms disappeared spontaneously after two biopsies. Of the 37 referred patients, 8 patients developed

**Table 3** Rates of recurrences after first D-PVNS treatment of the knee.

| Treatment | Number of patients | | Length of follow up, years (range) | | Number of recurrences (range) | | Average time to first recurrence, years (range) | |
|---|---|---|---|---|---|---|---|---|
| | Primary | Referred | Primary | Referred | Primary | Referred | Primary | Referred |
| Complete surgical synovectomy | 9[a] | 2 | 12.8 (2.83-48.7) | 28.8[b] | 0.44 (0-3) | 3.5 (2-5) | 14.1 (1.0-27.2) | 0.86[b] |
| Partial surgical synovectomy | 3 | 8 | 14.5 (6.6-26.7) | 14.1 (4.2-31.5) | 2 (1-4) | 2 (0-4) | 2.1 (1.2-2.7) | 2.4 (0.9-6.4) |
| Two-stage surgical synovectomy | 6 | 1 | 10.7 (2.9-17.1) | 12.1[b] | 1.3 (0-4) | 3[b] | 4.5 (1.0-10.5) | 0.9[b] |
| Surgical synovectomy completeness unknown | 4 | 15 | 21.8 (1.1-33.1) | 16.9 (5.3-43.0) | 1 (0-2) | 2.5 (1-5) | 10.7 (3.2-16.1) | 1.8 (0.3-7.7) |
| Yttrium | 1 | 6 | 19.2[b] | 13.1 (3.9-22.7) | 3 | 2.3 (1-7) | 3.3[b] | 0.6 (0.3-0.9) |
| Two-stage + Cryosurgery | 2 | 0 | 7.3 (6.1-8.5) | - | 0 | - | 0 | - |
| Two stage + EBRT | 2 | 0 | 4.3 (3.1-5.6) | - | 0 | - | 0 | - |
| Surgical synovectomy + Yttrium | 0 | 1 | - | 9.7[b] | - | 1 | - | 3.2[b] |
| Unknown or lost to follow-up | 0 | 4 | - | 6.2 (1.1-9.4) | - | 2 (0-4) | - | Data incomplete |

[a] One patient with a total knee replacement. [b] Data only available for one patient. EBRT: external beam radiotherapy. This table shows the difficulty of analyzing retrospective case series with this disease caused by multiple available treatments, as well as small patient groups with too little power for significance.

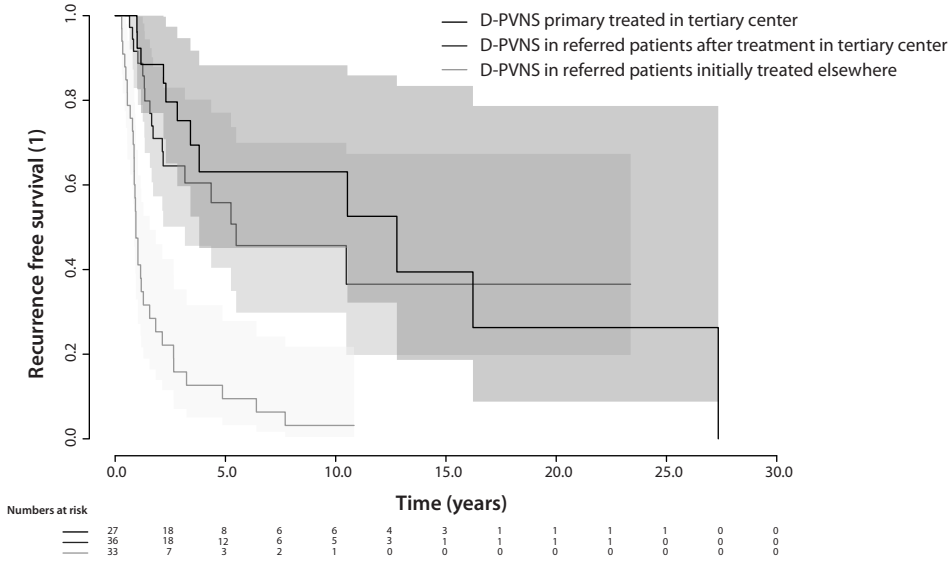
one recurrence and 26 had two or more recurrences (see supplementary table S1, available at *Rheumatology* Online). This last group contains all recurrences, including known recurrences treated elsewhere. Their mean follow-up was 14.6 years (range 1.1-43.0).

When only recurrences that occurred after treatment at our tertiary centre were considered in the referred patients, 16 patients had no recurrences, 5 patients had one recurrence and 6 patients had two or more recurrences. The mean follow-up was 12.1 years (range 1.6-38.5). Recurrences were treated by different (combinations) treatments, outlined in detail in supplementary table S1 (available at Rheumatology Online).

### Follow-up

The overall 1-, 5-, 10- and 15-year RFS for all D-PVNS knee patients was 68% (S.E. 6), 32% (S.E. 7), 25% (S.E.7) and 16% (S.E. 7), respectively (figure 1). The primary group had a 1- and 5-year RFS of 92% (S.E. 5) and 65% (S.E. 10), respectively. The referred patients had a 1- and 5-year RFS of 47% (S.E. 9) and 10% (S.E. 5), respectively.

**Figure 2** Kaplan-Meier curves showing recurrence-free survival for primary and referred diffuse pigmented villonodular synovitis.




Uncertainty is shown by 95% CI and a number-at-risk table below the graph. The referred patients are represented in two groups. One group shows recurrence-free survival from the initial treatment, the other shows recurrence-free survival after the initial treatment in a tertiary centre. Recurrences were more frequent for referred patients initially treated elsewhere. D-PVNS: diffuse pigmented villonodular synovitis.

The 1- and 5-year RFS for this last patient group from the first treatment at our centre until the last follow-up was 93% (S.E. 5) and 60% (S.E. 11), respectively (figure. 2).

### Complications

Perioperative complications after surgical excision of D-PVNS and their treatments are described in table 4. In only four patients did the complication occur after the initial treatment (see supplementary table S1, available at Rheumatology Online).

**Table 4** erioperative complications after surgical excision of diffuse pigmented villonodular synovitis.

| Complication | Number of patients | Treatment of complication (number patients) |
|---|---|---|
| Delayed wound heeling | 2 | Spontaneous recovery |
| Local paraesthesia | 1 | Spontaneous recovery |
| Stiffness | 5 | Manipulation under anaesthesia (1); adhesiolysis (1); clinical |
| Superficial wound infections | 4 | mobilizations (2); unknown (1) Antibiotics |
| Neurolysis | 1 | Unknown |
| Haematoma | 3 | Unknown |
| Deep wound infections | 2 | Surgical drainage |
| Percutaneous fistula | 1 | Unknown |

### Quality of life

SF-36 scores were obtained for 53% of D-PVNS knee patients, on average 10.1 years (range 2.4-28.8) after the first treatment. Table 2 shows the mean scores of all nine SF-36 scales. Compared with the general population[154], D-PVNS patients score significantly lower on physical functioning (P= 0.006), mental health (P= 0.02), vitality (P= 0.002) and general health (P < 0.001).

## Discussion

The limited available knowledge of the long-term outcome of PVNS treatment based on a few small studies and the lack of QoL measures motivated us to analyse our large patient group. We were able to identify 107 patients over the last 25 years. We retrospectively studied the treatment results of the knee patients by identifying recurrences, RFS, complications and QoL. These results were analysed by subgroup and primary or recurrent disease

### Diffuse pigmented villonodular synovitis

This study, with a long follow-up, shows an overall recurrence rate of 72% in D-PVNS of the knee. The recurrence rate was 44% for patients first treated at our institution and 92% for referred patients. Blanco et al.[39] reported a recurrence rate of 14% in 22 prospectively followed primary D-PVNS knee patients treated by partial arthroscopic synovectomy combined with radiation therapy. Their mean follow-up was 33 months (range 26-76). Flandry et al.[51] retrospectively reported an 8% recurrence rate of D-PVNS in 23 knee patients (19 primary, 4 recurrent) treated by complete synovectomy, with a mean follow-up of 58 months (range 20-126).

Chin et al.[55] described 40 patients with recurrent D-PVNS of the knee: 10 received a surgical synovectomy and the other 30 received additional external beam radiation therapy. The recurrence rate was 18% with a mean follow-up of 5 years (range 1.7-8). These three articles seem to show a trend towards the longer the follow-up, the greater the number of recurrences, corresponding to our results.

### Localized pigmented villonodular synovitis

Dines et al.[116] reported no recurrences in 84 primary L-PVNS patients, of whom 29 were excluded as they were incidental findings and only 26 of the remaining patients were evaluated. Our results show recurrence rates of 22% in 27 L-PVNS patients over an average 7.2 years. Two of them had already been treated elsewhere.

### Both subtypes mixed

Byers et al.[3] described recurrence rates of almost 50% over 3-35 years, however, both subtypes were combined and it is unclear whether only primarily affected patients were included. As in our patient group, their patients received different treatments, including synovectomies and external beam radiotherapy.

Other relatively large case series have analysed PVNS of the knee but did not differentiate between the two subtypes.[4,5,36,50,54] Recurrence rates of between 20% and 36% were reported in 25-75 patients with a mean follow-up of 0.3-13.5 years. For these studies it is not known whether these patients were primary or recurrent cases.

### Recurrence-free survival

Chiari et al.[75] reported 23 primary L-PVNS patients with a 1- and 5-year RFS of 100% and 88%, respectively, after surgical excision for all joints. For 19 primary D-PVNS patients they reported a 1- and 5-year RFS of 80% and 27%, respectively, after surgical excision. However, they combined different locations, like knees, hips and ankles, which can behave differently.[50,58] Hips are more affected at diagnosis, caused by more joint space.[50] The mean follow-up was 80 months (range 26-294).

Our analyses focused on the knee. We found an overall 1- and 5-year RFS of 83% and 69% for L-PVNS patients, respectively. For primary L-PVNS patients, this was 89% and 80%, respectively. Similar differences were found for D-PVNS patients, with an overall 1- and 5-year RFS of 68% and 32%, respectively, and 92% and 65%, respectively, for patients first treated at our centre. These results not only confirm the importance of discerning primary from recurrent patients in analyses, but it also underlines the possibility of a biologically aggressive subgroup. However, predictive markers for biologically more aggressive behaviour have not yet been found.

## Complications

The nature and number of complications agreed with the literature,[3,5,51,55] mostly consisting of infections and stiffness requiring manipulation. Not only the disease itself, but also its treatments, can cause loss of joint function. This is due to stiffness as a result of fibrosis, but also the development of OA. As a result, some patients even change career.

## Quality of life

We found a significant impact on QoL scores compared with the general population.[154] Both subgroups, L-PVNS and D-PVNS, scored low on mental health, vitality and general health compared with the general population.[154] The D-PVNS patients also scored low on physical functioning, which might be attributed to impaired joint function due to multiple treatments with or without complications. To our knowledge, there are no QoL measurements published for PVNS patients. The SF-36 questions were asked at various times after treatment and patients received various treatments, and because of the relatively small group, all ages were analysed together. Nevertheless, there were significant differences.

## Strengths and limitations

Related to the retrospective character of this study, there were missing data and some patients were lost to follow-up. However, a large number of PVNS patients were included and complete information regarding their treatments was available for all primary patients and almost complete for referred patients, including long-term follow-up.

Unfortunately, no information was available from patients who were treated first in other centres and had no recurrences. Our tertiary centre receives primary PVNS cases from other centres either centres that do not treat or because the patients are difficult to treat (i.e. patients with recurrences or with extensive disease). Therefore our results might be an overestimate. However, comparing our large series with published incidence numbers suggests we received most patients.[4]

In addition, our results show an increase in RFS of patients first treated at our centre compared with patients first treated elsewhere. The above mentioned emphasizes the importance of centralization of care for this rare disease. Centralization may result in an increase in patient numbers treated, thereby increasing experience with specific treatments, notable effects of treatments and quality of patient registration/ follow-up.

To the best of our knowledge, this is the first study that included QoL measures in PVNS patients. Measurement of QoL is increasingly important in today's health care. Further studies should demonstrate whether or not the decreased QoL in PVNS patients in the present study is a consequence of the disease itself or of the (multiple) treatment(s) the patients received. However, it should be noted that not all patients completed the SF-36 questionnaire (70% of the L-PVNS vs 53% of the D-PVNS patients). To get an estimate of potential non-response bias, values known from all patients (age, sex, follow-up time and type of PVNS) were compared with the values that prevailed in the subgroup of those who answered. No significant difference was found between the groups, indicating that there might be no non-response bias.

## Conclusions

Recurrence rates of PVNS deteriorate with time. Long follow-up rates underline that D-PVNS in particular is a continually recurring disease that over time is increasingly difficult to treat. Our findings confirm the importance of differentiating PVNS subtypes and also suggest that patients should receive treatment(s) at tertiary centres because of its rarity and destructiveness. Recurrence rates and RFS are not the only important measurements in this potentially disabling disease. The SF-36 is a useful tool, in addition to functional scores, to express treatment results. In order to design an optimal treatment, we have started a prospective study where clinical parameters, function and QoL are being studied at regular intervals pre- and postoperatively.

# 11

# The effect of surgery in Tenosynovial Giant Cell Tumours as measured by patient reported outcomes on quality of life and joint function

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*Authors contributed equally to this work.

The bone and joint journal 2018 Submitted.

## Abstract

To evaluate health-related quality of life (HRQoL) and joint function in TGCT patients before and after surgical treatment.

This prospective cohort study run in two Dutch referral centres, assessed patient-reported outcome measures (SF-36, VAS and WOMAC) in 359 consecutive patients with localized- and diffuse-type TGCT of large joints. Patients with recurrent disease (N=121) and a wait-and-see policy (N=32) were excluded. Collected data were analysed at specified time intervals pre-(baseline) and/or postoperatively up to 5 years.

In total 206, 108 localized- and 98 diffuse-type, TGCT patients were analysed. Median age at diagnosis of localized- and diffuse-type was 41 (IQR 29-49) and 37 (IQR 27-47) years, respectively. SF-36 analyses showed statistically significant and clinically relevant deteriorated preoperative- and direct postoperative scores compared with general population means, depending on subscale and TGCT subtype. After 6 months of follow up, these scores improved to general population means and continued to be fairly stable the following years. VAS scores, for both-subtypes, showed no clinically relevant differences pre- or postoperatively. Pain experience varied hugely between patients and also over time. WOMAC scores, for both TGCT subtypes, showed no clinically relevant differences pre- versus postoperatively. However, in diffuse-type patients WOMAC pain and physical function scores showed a trend towards improvement postoperatively.

Patients report a significant better HRQoL after surgery in TGCT whereas joint function showed a trend towards improvement. Pain scores –which vary hugely between patients and in patients over time- did not improve. A disease specific patient-reported outcome measure would help to decipher impact of TGCT on patients' daily life and functioning in more detail.

Level of evidence: 2

# Introduction

Tenosynovial giant cell tumours (TGCT) of large joints, historically known as pigmented villonodular synovitis (PVNS), are rare colony stimulating factor-1 (CSF-1)-driven proliferative, mono-articular disorders. They affect the joints or tendon sheaths at all ages, however mostly at young adulthood. It most commonly affects large, weight bearing joints such as knees, ankles and hips.[41,42] The incidence rate of localized-extremity (excluding digits) and diffuse-type TGCT is 10 and 4 per million person years, respectively.[18] Localized-type comprises a single nodule and has a favourable course after surgical treatment. Diffuse-type involves the synovial lining as well as surrounding structures. It can behave locally aggressive and is challenging to remove completely. There is a significant risk of recurrence after surgical treatment (>50% depending on follow up times).[1,42,68]

Diffuse-type TGCT often requires one or multiple synovectomies, or at times a joint replacement, and rarely even amputation.[41-43] In patients with extensive and/or recurrent TGCT, other available treatment modalities include radiation synovectomy[46], external beam radiation therapy[47], and cryosurgery[174] of which the effects are controversial.[76] More recently, systemic therapy has been introduced, targeting the CSF-1 receptor. At first treatment with the multi targeting tyrosine kinase inhibitor imatinib started, very recently more promising data of a CSF-1 specific targeting agent were presented.[16,65,255] Systemic treatment may need to be given for one to several years, but the optimal treatment duration has still to be determined. Despite the variety of treatments, it is unclear which one is the most effective with the least impact on quality of life.

A limitation of most clinical TGCT studies is the absence of disease specific and validated patient-reported outcome measures (PROMs) to document disease and treatment related functioning and symptomatology. Overall survival is the primary endpoint in oncologic clinical trials, however this is not appropriate for TGCT, which is rarely lethal.[71] Alternate treatment endpoints in TGCT include response rates, progression free survival, and avoidance of morbid therapies. As indicated, quality of life (QoL) and functional scores are of utmost importance, but they are mostly not reported or only described for small, heterogeneous patient groups.[20,42] The impact of therapies and the relevance of treatment outcomes to patients' quality of life is therefore essential especially in a benign but locally aggressive disease.[72,66]

The aim of our study is to investigate HRQoL, pain and joint function in surgically treated non-recurrent TGCT patients, pre- and/ or postoperatively over time.

## Methods

This prospective cohort study was conducted at two Dutch referral centres; Radboud University Medical Center (RadboudUMC) and Leiden University Medical Center (LUMC). Between 2011 until 2018 patients diagnosed with primary therapy-naïve or recurrent TGCT (magnetic resonance imaging (MRI) and histological confirmed) of large joints, were asked to participate. Large joints were defined as all joints except the digits. Three hundred and fifty-nine consecutive patients were identified; 136 (38%) with localized TGCT, 223 (62%) with diffuse TGCT. During regular outpatient clinic visits, patients who consented were requested to complete PROMs questionnaires. To further reduce heterogeneity of the group, patients with recurrent disease at presentation, treated conservatively (wait-and-see policy) and patients in absence of QoL and function scores after primary surgery, were excluded from this analysis (figure 1). Also, if patients developed relaps after surgical treatment, they were excluded from this time on. Hundred-and-eight localized- and 98 diffuse-type therapy-naïve patients were used for final analyses (figure 1).

The study protocol (RadboudUMC (file number CMO 2012/555) and LUMC (file number CMO P13.029)) was approved by the local institutional ethical review boards and was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent. Patients provided written informed consent when they completed questionnaires (SF-36, VAS and WOMAC).

The used PROMs included the Dutch translation of a generic HRQoL instrument, the 36-item Short Form Health Survey (SF-36)[154], a Visual Analog Scale (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). SF-36 is an instrument for measuring general health, including eight subscales: Physical functioning (PF), Social functioning (SF), Role limitations due to physical problems (RP), Role limitations due to emotional problems (RE), General mental health (MH), Vitality (VT), Bodily pain (BP) and General health (GH). SF-36 scores were computed by summing the item scores and transforming the scores onto a 100-point scale (0= “worst health” and 100= “best health”). VAS for worst pain was used to estimate patients pain intensity of the affected joint for the past 24 hours, using a series of 0- to 10-point (0= “no pain” and 10= ”pain as bad as you can imagine”).[256] The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to evaluate affected joint function.[156] The WOMAC is a 24-item instrument assessing pain, stiffness and difficulty performing daily activities originally designed for osteoarthritis. All items are measured on a 5 point scale; ranging from “no” up to “worst imaginable”. The WOMAC data were standardized to a range of values from 0-100, for which lower values indicate more

pain, more stiffness, or worse physical functioning. Gelhorn et al. [72] used a modified version of WOMAC for TGCT patients.

Patient demographics and clinical, histological, radiological, treatment and follow-up data were extracted from individual patients' files at each institution by the local investigator (FGMV or MJLM) and were provided in an anonymous form for analyses. Definitive histological diagnosis was performed at the centre of origin by dedicated pathologists with extensive experience in mesenchymal tumours. Recurrences and PROMs were analysed according to TGCT subtype. Data were described using percentages for qualitative variables and medians with interquartile ranges (IQR) for continuous variables.

As patient questionnaires were completed at different points in time they were categorized in the following time intervals: pre-surgery (=0 or baseline), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months. At final analyses we did not have questionnaires in all time intervals for each individual patient, some had solely pre- or post-operative scores. In case of recurrent disease after primary treatment in a therapy-naïve patient, QoL and functions scores were used up to recurrence development, confirmed on MR imaging. Follow-up time was defined as the period between first TGCT confirmation (MR imaging and histologic) and most recent patient contact. Time to recurrence was calculated as time from first treatment until proven (MR imaging and histologic) first recurrent disease.

Differences between QoL scores (SF-36, VAS, WOMAC) were tested using t-tests. SF-36 scores were compared with Dutch general population scores[154], and WOMAC and VAS baseline (preoperative) scores were compared with postoperative scores.

To estimate the clinical relevance, the mean differences were compared with the minimal clinically important difference (MCID). MCID is a QoL measure that represents the smallest difference or change beyond statistical significance in an outcome measure score that would be considered clinically relevant by the value patients place on change.[257] The MCID for SF-36 has been estimated at to be 10 points by Escobar et al[258] in patients undergoing total knee replacement. For VAS pain a MCID of 2 was used.[259] The MCID for standardized WOMAC values has been estimated at around 15-20 points[258], with relative improvements of 21-41% for its subscales[259-261]. We used a MCID for WOMAC of 20 points based on consensus in the project team and the study of van der Wees et al.[262]

All statistical analyses were performed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). P-values <0.05 were considered statistically significant.

# Results

## Patients

After exclusion of patients with recurrent disease (N=121) and patients with a wait-and-see policy (N=32), 206 patients remained for further analyses (figure 1). Median age at diagnosis of localized- (N=108) and diffuse-type (N=98) TGCT was 41 (IQR 29-49) and 37 (IQR 27-47) years, respectively. The majority of patients were female (localized N=62 (57%)), had diffuse-type TGCT N=64 (65%)), and had the knee as the most common affected joint in both subtypes (localized N=84 (78%)) and diffuse N=72 (74%)). Pain (localized N=61 (57%) and diffuse N=58 (60%)) and swelling (localized N=66 (61%) and diffuse N=65 (67%)) were the most prevalent clinical symptoms at diagnosis for both subtypes (Table 1).

## Treatments

As primary treatment, three (3%) localized-type patients were treated with arthroscopic synovectomy, 103 (95%) with one-staged synovectomy and two (2%) with (endo-)prosthesis. Seven patients (6%) had a first recurrence after median 2.9 (2.1-5.6) years. Overall median follow up of localized therapy-naïve patients was 2.0 (IQR 0.7-4.6) years. At final follow up, 104 (96%) patients had no evidence of disease, 4 (4%) patients were alive with disease, without planned treatment.

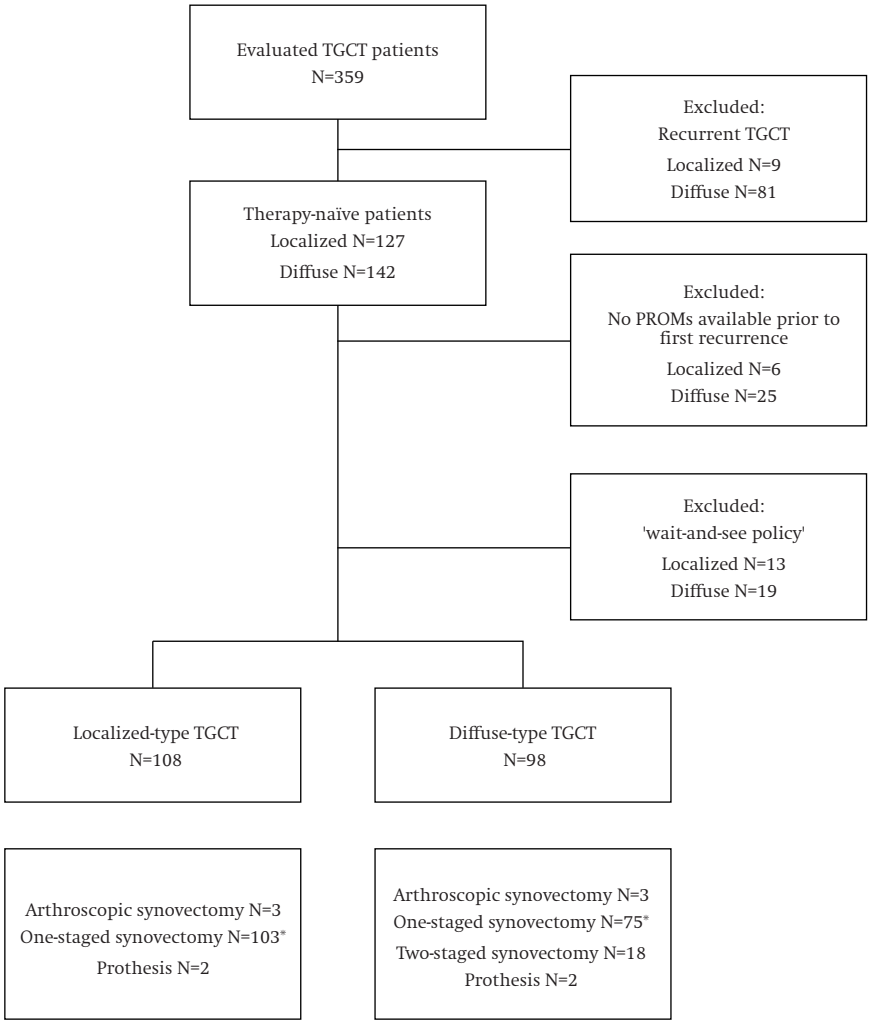
Diffuse-type patients were treated with arthroscopic (N=3 (3%)), one-staged (N=75 (76%)) or two-staged (N=18 (19%)) synovectomy. Two patients received an (endo-) prosthesis. Twenty-seven patients (28%) had a first recurrence after median 1.3 (1-3) years, thereafter they were excluded from further analyses. Overall median follow up of diffuse-type patients was 2.7 (IQR 1.4-4.9) years. At final follow up, 70 (71%) patients had no evidence of disease, 27 (28%) patients were alive with disease and one patient died of another disease.

## HR Quality of life

Compared to Dutch general population means,[154] localized-type patients preoperatively scored significantly lower on PF (13.2(95%CI 6.0-20.5)), SF (18.7(95%CI 10.3-27.2)), RP (25.8(95%CI 11.9-39.8)), RE (20.6(95%CI 7.3-34.0)) and BP (21.2(95%CI 12.7-29.8)). These differences were also clinically relevant (mean difference > MCID 10). This effect lasted up to 3 months postoperatively on RP (40.1(95%CI 16.7-63.5)) and BP(17.2 (95%CI 2.2-32.1)). Thereafter, these means improved to general population means and continued fairly stable during the following years.

Diffuse-type patients preoperatively scored statistically significant and clinically relevant (mean difference > MCID 10) lower on PF (23.7(95%CI 16.7-30.8)), SF (15.6(95%CI 8.8-22.5)), RP (37.4(95%CI 25.3-49.5)), VT (10.0(95%CI 3.5-16.4)) and BP (21.6(95%CI 14.7-28.5)) compared to general population means. This difference

**Figure 1** Flowchart of consecutive patients with TGCT, included for quality of life analyses.




*Additional cryosurgery in two localized- and five diffuse-type TGCT patients

**Table 1** Characteristics of therapy-naïve TGCT patients.

| | Localized N (%) | Diffuse N (%) |
|---|---|---|
| Total | 108 | 98 |
| Median age at diagnosis (IQR), yrs. | 41 (29-49) | 37 (28-47) |
| Sex | | |
| Male | 46 (43) | 34 (35) |
| Female | 62 (57) | 64 (65) |
| Tumor localization | | |
| Knee | 84 (78) | 72 (74) |
| Ankle | 10 (9) | 10 (10) |
| Hip | 1 (1) | 7 (7) |
| Other | 13 (12) | 9 (9) |
| Pre-surgery symptoms | | |
| Pain | 61(57) | 58 (60) |
| Swelling | 66 (61) | 65 (67) |
| Loss of function | 8 (7) | 20 (21) |
| Stiffness | 5 (5) | 14 (14) |
| Recurrent disease | | |
| No | 101 (94) | 71 (72) |
| Yes | 7 (6) | 27 (28) |
| Median time to first recurrence (IQR) | 2.9 (2.1-5.6) | 1.3 (1-3) |
| Complications | | |
| None | 106 (98) | 91 (93) |
| Deep wound infection | - | 2 (2) |
| Superficial wound infection | 1 (1) | 2 (2) |
| Hemorrhage | - | 1 (1) |
| Joint stiffness | 1 (1) | 1 (1) |
| Neurovascular damage | - | 1 (1) |
| Median follow up time (IQR), yrs | 2.0 (0.7-4.6) | 2.7 (1.4-4.9) |

Abbreviations: TGCT= Tenosynovial Giant Cell Tumors, N= Number of patients, mo=months, yrs= years, IQR= inter quartile range, other= Foot, shoulder, elbow, wrist or temporomandibular joint, AWD= alive with disease.

with the general population remained significant for up to 3 months postoperatively on PF (21.9(95%CI 5.0-38.8)), SF (19.9(95%CI 3.0-36.9)), RP (40.1(95%CI 16.2-64.1)), VT (13.0(95%CI 1.5-24.5)) and BP (22.4(95%CI 5.3-39.4)) and up to 6 months postoperatively on PF (14.8(95%CI 3.3-26.4)). Thereafter, the mean SF-36 scores of diffuse-type patients improved to Dutch general population means and continued fairly stable the following years. Compared to general population means diffuse-type patients scored statistically significant and clinically relevant lower on GH 3-6 months (10.6(95%CI 9.8-23.2)), 6-12 months (10.3(95%CI 2.3-18.9)) and 24-36 months (10.7(95%CI 4.5-16.9)) postoperatively.

### Visual analog scale for pain

No statistical significant nor clinical relevant difference in pain scores were found in localized-type patients preoperatively (median VAS score 4, IQR 1-6) versus 3 months postoperatively (median VAS score 3.5, IQR 1-5), which in fact remained the same up to five years follow up. Median VAS scores in diffuse-type patients showed no clinical relevant difference preoperatively (median VAS score 4, IQR 2-6) versus 3 months postoperatively (median VAS score 2, IQR 1-4), and also here the scores remained the same up to five years follow up. Pain experience in both subtypes TGCT varied widely between and within patients over time (range 0-7 years follow up).

### Joint function

Mean WOMAC scores on pain, stiffness and physical functioning for both localized- and diffuse-type patients showed no significant differences pre-(baseline) versus postoperatively. Patients of both subtypes scored significantly better at some postoperative time intervals compared to baseline scores, however mostly clinically irrelevant (mean difference < 20) (table 3a and b).

In diffuse-type patients (table 3b) WOMAC pain and physical function scores showed a trend towards improvement in scores from preoperatively (baseline) to postoperative up to 5 years follow-up.



## Discussion

To our knowledge, this study provides the largest prospective cohort, including longest follow up time, to report on PROMs in therapy-naïve patients with localized- and diffuse-type TGCT of large joints followed up until relapse of disease or end of study. In both TGCT subtypes HRQoL (SF-36) was statistically significant and clinically relevant decreased before surgical treatment on the main physical domains (RP, PF, BP) and some mental domains (SF, RE, VT) compared to general

**Table 2a** SF-36 scores of localized-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up compared with general population means.

| SF-36 subscales | General population (mean (SD)) | Time intervals in months | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 N=42 | 0-3 N=14 | 3-6 N=11 | 6-12 N=15 | 12-24 N=16 | 24-36 N=15 | 36-48 N=10 | 48-60 N=8 |
| Physical functioning (PF) | 81.9 (23.2) | 68.7* (23.0) | 67.1 (23.8) | 69.1 (22.6) | 74.3 (16.7) | 78.8 (19.9) | 77.0 (17.9) | 73.0 (33.0) | 75.6 (23.7) |
| Social functioning (SF) | 86.9 (20.5) | 68.2* (26.9) | 81.3 (22.3) | 87.5 (17.7) | 80.0 (22.1) | 85.9 (19.3) | 83.3 (21.5) | 71.3 (27.7) | 76.6 (29.5) |
| Role physical (RP) | 79.4 (35.5) | 53.6* (44.7) | 39.3* (43.5) | 56.8 (40.5) | 66.7 (38.6) | 78.1 (36.4) | 71.7 (32.6) | 72.5 (41.6) | 71.9 (38.8) |
| Role emotional (RE) | 84.1 (32.3) | 63.5* (42.8) | 88.1 (28.1) | 81.8 (40.5) | 86.7 (27.6) | 77.1 (35.9) | 88.9 (24.1) | 90.0 (31.6) | 83.3 (35.6) |
| Mental health (MH) | 76.8 (18.4) | 70.1 (18.9) | 79.4 (17.5) | 83.3 (14.3) | 85.6 (15.3) | 74.8 (17.3) | 81.1 (11.3) | 83.2 (11.9) | 80.5 (19.4) |
| Vitality (VT) | 67.4 (19.9) | 60.6 (20.9) | 66.2 (20.4) | 67.3 (23.4) | 73.3 (18.4) | 60.9 (14.2) | 69.0 (16.9) | 61.5 (24.7) | 63.8 (25.0) |
| Bodily pain (BP) | 79.5 (25.6) | 58.3* (27.3) | 62.3* (27.8) | 71.1 (25.8) | 69.5 (18.9) | 74.7 (25.3) | 71.7 (24.1) | 72.8 (33.0) | 71.3 (33.4) |
| General health (GH) | 72.7 (22.7) | 66.4 (18.3) | 65.0 (14.1) | 73.2 (15.2) | 67.7 (16.4) | 64.4* (15.4) | 70.0 (17.7) | 63.5 (22.1) | 65.0 (15.1) |

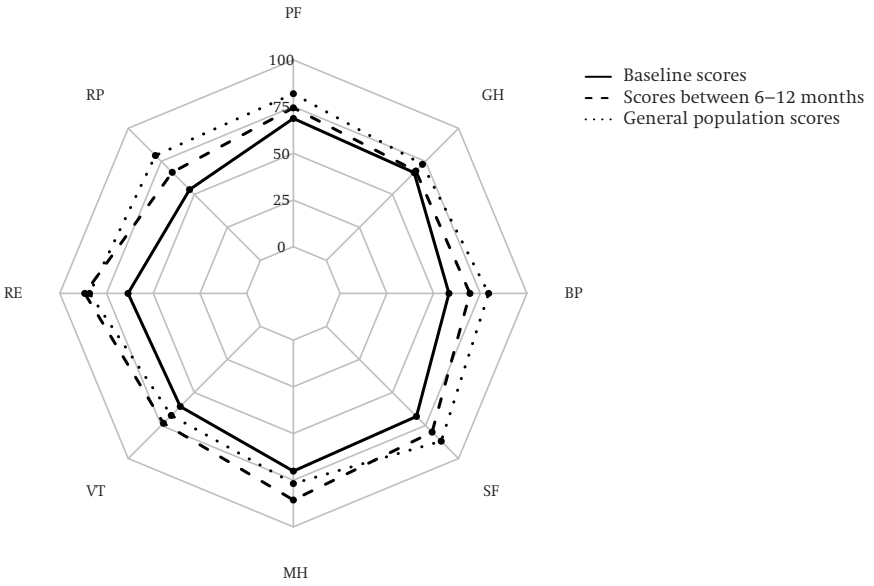
N= number of questionnaires. *=statistically significant, underlined scores are clinically relevant (mean difference > MCID 10). SF-36 questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

**Table 2b** SF-36 scores of diffuse-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up compared with general population means.

| SF-36 subscales | General population (mean (SD)) | Time intervals in months | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 N=47 | 0-3 N=14 | 3-6 N=17 | 6-12 N=17 | 12-24 N=17 | 24-36 N=15 | 36-48 N=15 | 48-60 N=13 |
| Physical functioning (PF) | 81.9 (23.2) | 58.2* (23.7) | 60.0* (31.6) | 67.1* (23.6) | 79.4 (12.0) | 71.8 (22.2) | 72.3 (18.9) | 73.3 (25.0) | 79.6 (17.1) |
| Social functioning (SF) | 86.9 (20.5) | 71.3* (23.2) | 67.0* (31.6) | 75.0 (25.8) | 85.3 (14.8) | 88.2 (16.8) | 85.8 (16.3) | 82.5 (27.9) | 86.5 (15.7) |
| Role physical (RP) | 79.4 (35.5) | 42.0* (40.7) | 39.3* (44.6) | 60.3 (44.2) | 85.3 (28.0) | 75.0 (36.4) | 70.0 (40.3) | 78.3 (37.6) | 90.4 (16.3) |
| Role emotional (RE) | 84.1 (32.3) | 72.3 (40.1) | 78.6 (38.4) | 86.3 (29.0) | 92.2 (18.7) | 82.4 (35.6) | 93.3 (18.7) | 84.4 (35.3) | 92.3 (20.0) |
| Mental health (MH) | 76.8 (18.4) | 71.0 (18.4) | 74.3 (15.6) | 78.4 (14.0) | 78.4 (16.3) | 75.8 (20.1) | 78.4 (14.9) | 74.9 (22.0) | 77.8 (18.6) |
| Vitality (VT) | 67.4 (19.9) | 57.4* (21.8) | 54.4* (21.4) | 62.4 (21.1) | 71.2 (19.9) | 61.2 (23.0) | 63.7 (18.8) | 66.3 (28.4) | 65.4 (23.5) |
| Bodily pain (BP) | 79.5 (25.6) | 57.9* (23.1) | 57.1* (31.7) | 70.0 (22.3) | 77.9 (17.0) | 77.2 (23.0) | 70.0* (16.9) | 76.0 (22.5) | 79.4 (22.1) |
| General health (GH) | 72.7 (22.7) | 63.9* (13.6) | 63.6 (19.1) | 62.9* (13.6) | 62.1* (16.9) | 62.4* (19.9) | 62.0* (11.6) | 65.7 (17.3) | 66.9 (15.2) |

N= number of questionnaires. *=statistically significant, underlined scores are clinically relevant (mean difference > MCID 10). SF-36 questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

**Figure 2A** SF-36 scores of localized-type, therapy-naïve, TGCT patients

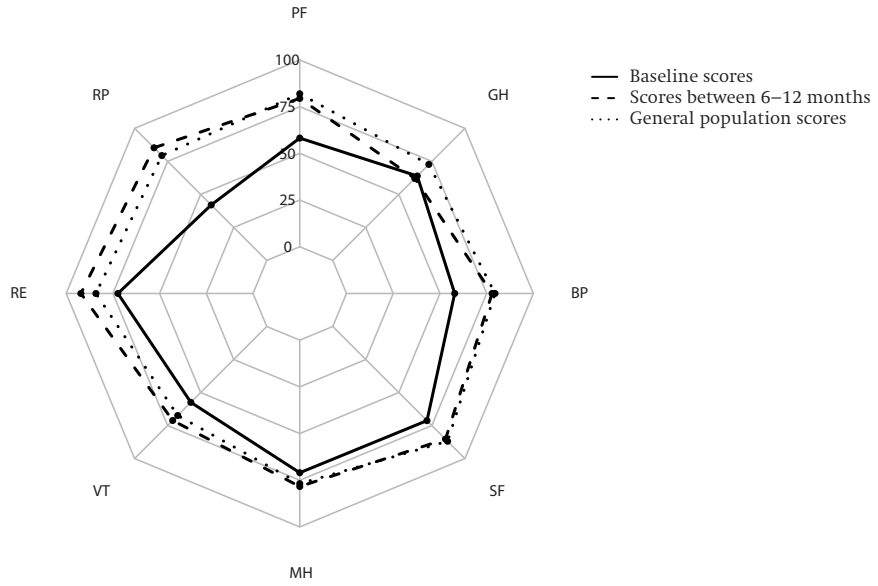



Spider plot showing SF-36 scores preoperative (baseline), 6-12 months postoperatively and of Dutch general population means[153]: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), general mental health (MH), vitality (VT), bodily pain (BP) and general health (GH).

population means. These low scores lasted for up to 6 months postoperatively depending on TGCT subtype and SF-36 subscale. Thereafter, all SF-36 subscales improved to general population means and continued fairly stable the following years. Pain experience (VAS) in both subtypes varied widely between and within patients over time. Mean function (WOMAC) scores on pain, stiffness and physical functioning for both subtypes TGCT showed no clinically relevant difference pre-(baseline) versus postoperatively. However, in diffuse-type patients WOMAC pain and physical function scores showed a trend towards improvement in scores from preoperatively (baseline) to postoperatively up to five years follow-up.

TGCT can behave locally aggressive causing joint destruction and provoke significant pain, swelling, decrease in range of motion, and stiffness.[16] This morbidity can lead to impairment of HRQoL and function because of pain, medication use, disability, the knowledge of having a tumour (despite its benign character), and loss of working hours.[72] To improve these consequences, treatments

**Figure 2B** SF-36 scores of diffuse-type, therapy-naïve, TGCT patients




Spider plot showing SF-36 scores preoperative (baseline), 6-12 months postoperatively and of Dutch general population means[153]: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), general mental health (MH), vitality (VT), bodily pain (BP) and general health (GH).

are performed, which –unfortunately- might contribute to further joint destruction.[76] The prolonged course of the disease and the need for multiple surgeries has been reported to result in a worse joint function for many patients.[11] In addition to the physical and financial burden for the patient, TGCT also involves high healthcare burden.[6] Finding an efficient treatment is important.

This study reported on the loss of HRQoL in patients with TGCT compared to general population means. The improvements in HRQoL after surgical resections were present 3-6 months after surgery. This could be explained by the morbidity of an operation and the associated recovery time.

We did not find statistically significant and clinically relevant differences in pain experience. This might be explained by a variability in symptom experience as described by Gelhorn et al.[72] They found that not all patients experience all symptoms and there was variability in how patients experienced symptoms within and among days.

**Table 3a** WOMAC scores of localized-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up.

| WOMAC scores (mean (SD)) | Time intervals in months | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0<br>N=35 | 0-3<br>N=12 | 3-6<br>N=9 | 6-12<br>N=14 | 12-24<br>N=9 | 24-36<br>N=8 | 36-48<br>N=5 | 48-60<br>N=5 |
| Pain | 73.1<br>(20.9) | 74.2<br>(17.4) | 86.7*<br>(13.7) | 83.9<br>(16.5) | 70.0<br>(22.4) | 85.0*<br>(11.0) | 81.0<br>(29.2) | 95.0*<br>(5.0) |
| Stiffness | 73.5<br>(25.1) | 59.4<br>(19.3) | 77.8<br>(21.4) | 79.5<br>(25.8) | 59.7<br>(32.3) | 67.2<br>(25.8) | 85.0<br>(22.4) | 80.0<br>(11.2) |
| Physical | 75.0<br>(21.4) | 76.5<br>(19.4) | 88.1*<br>(13.1) | 89.8*<br>(11.8) | 74.7<br>(20.6) | 86.0<br>(11.6) | 82.1<br>(33.9) | 92.6*<br>(7.1) |
| Total | 74.7<br>(20.1) | 74.6<br>(17.8) | 87.4*<br>(13.5) | 87.7*<br>(13.0) | 72.5<br>(21.3) | 84.2<br>(10.6) | 82.1<br>(31.8) | 92.1*<br>(6.6) |

WOMAC= standardized Western Ontario and McMaster Universities Osteoarthritis Index. In the standardized WOMAC (0-100) sum scores, higher values indicate less pain, stiffness or better physical functioning. N= number of questionnaires.*=statistically significant, underlined scores are clinically relevant (mean difference > MCID 20). WOMAC questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

**Table 3b** WOMAC scores of diffuse-type, therapy-naïve, TGCT patients preoperatively and postoperatively up to 5-years follow up.

| WOMAC scores (mean (SD)) | Time intervals in months | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0<br>N=31 | 0-3<br>N=11 | 3-6<br>N=10 | 6-12<br>N=9 | 12-24<br>N=12 | 24-36<br>N=11 | 36-48<br>N=10 | 48-60<br>N=9 |
| Pain | 59.8<br>(20.9) | 68.2<br>(23.5) | 73.5<br>(17.2) | 75.6<br>(21.0) | 79.6*<br>(22.7) | 77.7*<br>(20.8) | 77.5*<br>(22.8) | 85.0*<br>(21.2) |
| Stiffness | 60.9<br>(24.1) | 62.5<br>(17.7) | 76.3<br>(24.6) | 69.4<br>(19.9) | 68.8<br>(22.3) | 69.3<br>(18.8) | 72.5<br>(21.1) | 75.0<br>(25.8) |
| Physical | 63.9<br>(18.8) | 68.3<br>(18.7) | 73.7<br>(22.2) | 82.7*<br>(15.7) | 81.0*<br>(23.1) | 76.7<br>(21.5) | 82.1*<br>(18.2) | 84.2*<br>(19.5) |
| Total | 62.8<br>(18.7) | 67.8<br>(18.4) | 73.9<br>(20.3) | 80.1*<br>(16.1) | 79.7*<br>(22.4) | 76.3<br>(20.2) | 80.3*<br>(18.0) | 83.6*<br>(19.4) |

WOMAC= standardized Western Ontario and McMaster Universities Osteoarthritis Index. In the standardized WOMAC (0-100) sum scores, higher values indicate less pain, stiffness or better physical functioning. N= number of questionnaires.*=statistically significant, underlined scores are clinically relevant (mean difference > MCID 20). WOMAC questionnaires were categorized in the following time intervals: pre-surgery (0), post-surgery after 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60 months.

The lack of clinically relevant improvement in joint function (WOMAC) could be explained by the destruction the disease already caused, or by the small number of questionnaires left after exclusion of many patients to optimize the homogeneity of the patient group. The lack of disease specific instruments to evaluate adequate PROMs for TGCT, may have led to underreporting disease specific issues.

SF-36 was developed to get more general insight into patients' health and as a means of making comparisons across conditions.[263] VAS was developed as a pain assessment tool used for cancer patients.[256] The WOMAC was originally developed to evaluate the outcome of a total knee replacement in patients with osteoarthritis.[156] SF-36, VAS and WOMAC are a good start in assessing the patients perspective in TGCT, since they are validated, easy to apply and globally known. These measures are frequently used for other diseases, allowing to compare TGCT patients with other patient groups, for example patients with joint replacements for osteoarthrosis.[108,258,264] Gelhorn et al. investigated 'patient-reported symptoms of TGCT'. They concluded that pain (VAS), swelling, stiffness and impaired joint function (WOMAC) are important PROMs.

Van der Heijden et al. [20] evaluated 30 patients with therapy-naïve and recurrent diffuse-type TGCT at a mean of 8 (range 2-32) years after diagnosis. HRQoL impairment (SF-36) was seen in all patients initially treated with arthroscopic synovectomy (62 range 26-94) and an open synovectomy (80 range 63-98), compared to healthy controls.[20] The patient population was small and heterogeneous, in which outcome measures were assessed at different time points after treatment. In the study of Verspoor at al.[42], which experienced similar limitations, HRQoL (SF-36) scores were not significantly different between localized- and diffuse-type TGCT. However, both patient groups had impaired HRQoL compared to general population means one the general health subscale. Diffuse patients also scored significantly lower on other subscales (PF, MH and VT). The current study, with a more homogenous, larger patient cohort and measurements at categorized time intervals, showed a similar impairment in therapy-naïve patients on PF pre-operatively for both subtypes and up to 6 months postoperatively in diffuse-type patients who generally need more extensive surgery compared to localized-type TGCT.

Case series reporting on joint function before treatment often included both subtypes, various localizations, a mixture of therapy-naïve and recurrent TGCT including multiple treatments.[11,20,80,132,265] Therefore, it is extremely challenging to perform a meta-analysis to prove treatment effect(s) in the rare disease TGCT. Through the emergence of systemic treatments for TGCT, attention for additional outcome measures besides recurrences has been raised, such as HRQoL and joint function. International cooperation has been initiated, resulting in large registries including QoL and joint function.[266] In the recent years targeted therapy has been

added to the armamentarium. At ASCO 2018 results of pexidartinib (PLX3397)[65], a selective inhibitor of CSF-1 receptor, KIT, and FLT3-ITD, were promising in a randomized, placebo controlled, phase 3 study. Pexidartinib compared to placebo resulted in an significantly improved overall response rate (39.3% vs 0%) and PROMIS physical function (4.06 vs 0.89), after a median 6 months follow up.[65] In this study range of motion, PROMIS physical function, worst stiffness and pain response were secondary endpoints. [65]

The joint localization of TGCT might influence physical function.[59,267] Therefore, a sensitivity analysis was performed on our patients with TGCT affecting the knee, which showed similar results to our primary analysis. In a univariate analyses on TGCT locations with recurrent disease as outcome, Palmerini et al.[38] did not find a difference between knees, hips and ankles.

Two crowdsourcing studies[21,268], using an online patient support-group, reported on physical function and HRQoL in TGCT patients. In patients with diffuse-type TGCT, recurrences requiring repeated surgery and joint replacement were reported to have a lower HRQoL and functional outcome.[21,268] Because of selection bias, it is possible that severe cases including (additional) recurrences were more likely to be online to complete the e-survey. However, all studies, including the current one suggest an impaired effect on HRQoL and function in patients with TGCT. The challenge remains to find the exact quantification method.

This study has some limitations that need to be discussed. Because of the rarity of TGCT, it is challenging to perform a prospective study with adequate patient numbers. To reduce heterogeneity of the patient group, we chose to exclude recurrent patients, at the expense of decreasing patient numbers. Still, heterogeneity in severity and duration of illness remained.

Selection bias should be taken into account, because this study only contains patients from two tertiary Dutch referral centres. Overrepresentation of extensive disease, could have resulted in an overestimation of the impact on HRQoL and joint function. Also, patients with complaints more often visit the outpatient clinic completing questionnaires. These patients might have more extended, metastatic, disease. By excluding patients with recurrent TGCT, this possible bias was reduced. On the contrary, patients who do well, like localized-type TGCT patients, were discharged early reducing their follow up time and number of questionnaires.

It should be noticed that HRQoL and function scores were taken at variable points after treatment for individual patients, which reduced numbers at some specific time points. Not all patients had preoperatively and postoperative available measures, causing an increase in the range of these outcome measures. Furthermore, it is preferred to adjust SF-36 measures for age, because of physiolog-

ically declined HRQoL and joint function decrease in ageing.[154,254]In the current study correction for age could not be achieved by differences in ages per time interval and the age distribution within time intervals.

Patients with localized-type TGCT generally do not have a high burden of their disease. The question is whether PROMs are essential in patients with localized disease, who can generally be treated curatively with a radical excision and are not eligible for systemic therapy. To date, surgical resection remains the treatment of choice for TGCT, but is associated with high recurrence rates and multiple additional surgeries in diffuse-type disease.[76] The balance between increased morbidity of multiple or invasive surgeries[20,77], alternative therapeutic options, and daily symptoms of the tumour is challenging. A more aggressive resection or other multimodality treatments, such as external beam radiation therapy, may adversely affect QoL, joint function and the development of osteoarthrosis, which are, given the young adult age group, factors of major importance.[38,42] Use of a control group and of specific and validated PROMs will better document treatment-induced symptomatic, functional and economic (back to work) consequences of these treatments.[72]

When systemic treatments show tumour growth arrest and symptomatic improvements, a less invasive approach would be justified.[16] The recent studies on targeted therapy used a control group and as secondary outcome measure PROMIS physical function.[65]

These measures are critical endpoints in demonstrating clinical relevance and impact of treatments for benign diseases in which death is no outcome variable.[72] Clinical benefit necessitates objective measures to correlate with tumour reduction. When significant changes in TGCT specific developed outcome measures are found, one should try to specify if this is the consequence of the disease itself, of the 'multiple' treatment(s) received, or of other factors, such as comorbidities, the knowledge of having a tumour or issues not related to disease.



## Conclusion

Patients report a significant better HRQoL after surgery in TGCT whereas joint function showed a trend towards improvement. Pain scores –which vary hugely between patients and in patients over time- did not improve. A disease specific patient-reported outcome measure would help to decipher impact of TGCT on patients' daily life and functioning in more detail.

# 12

## Summary

The aim of this thesis was to investigate the incidence, diagnosis, treatment options and outcome parameters in patients with TGCT of the joints. In **chapter 1**, an overview of the current knowledge was presented. TGCT are rare benign tumours arising from the synovium, tendon sheaths or bursae, and are divided into two known subtypes; localised (either digits or extremities) and diffuse. Our understanding of TGCT incidence was previously based on one single-country (US) study in 1980, which indicated annual incidences of 9 and 2 per million people for the localised (including digits) and diffuse-type TGCTs, respectively.

## Incidence

The nationwide study presented in **chapter 2** utilised five years of data obtained from the Dutch Pathology Registry (PALGA), from which worldwide incidence rates in the digits, localised-extremity and diffuse-type TGCTs were calculated to be 29, 10 and 4 per million person-years, respectively. TGCT is still a rare condition, but these results show it is a more common disease than was previously reported. Both types showed a predilection for the knee joint, a slight predisposition in females (male:female ratio 1:1.5), a median age at first treatment of 47 years, and for both types, patients were primarily treated with an open resection.

The research presented in **chapter 3** reviewed all published paediatric cases in 1990–2016, incorporated data from children younger than 18 years of age taken from the nationwide TGCT incidence study in **chapter 2**, and used clinical data from our nationwide bone and soft tissue tumour data registry from 1995–2015 to evaluate TGCT in children. A standardised paediatric TGCT incidence rate of 2.4 and 1.1 per million person-years was found in localised- (excluding digits) and diffuse-type TGCTs, respectively. The symptoms in both children and adults were swelling, pain and a limited range of motion. The median diagnostic delay (initial clinician consultation until diagnosis) was 12 (range: 1–72) months. No differences were found between children and adults in terms of the sex ratios of patients, symptoms, first treatment, recurrent disease, follow-up status, or median time to follow up.



## Diagnosis

MRI is the most discriminate imaging technique in diagnosing, preparing for surgery (evaluating the extent of disease) and evaluating TGCT during the follow up. MRI can reveal the conspicuous nodular (localised) or villous proliferation of the synovium (diffuse); however, no discriminating features describing or quantifying

tumour extent in relation to clinical outcome had previously been reported. Uniform MRI descriptions are important for clinical and research purposes; therefore, potentially distinguishing MRI parameters for assessing the extent of disease were defined and tested by field experts in **chapter 4.** These included the type of TGCT, articular involvement, cartilage-covered bone invasion, and the involvement of muscular/tendinous tissue, ligaments or neurovascular structures. With the exception of cartilage-covered bone invasion and neurovascular involvement, these parameters were evaluated in two different study populations to establish four TGCT severity subgroups based on the risk of recurrence. The proposed TGCT severity classification informs physicians and patients about the extent of disease and the risk of recurrence after surgical treatment. By defining the most severely affected patients (those with the highest risk of disease recurrence), the patients eligible for other treatment modalities could be identified and properly evaluated as part of a more homogenous patient population.

## Treatments

At present, the treatment strategy for patients with localised- and diffuse-type TGCTs in large joints is a surgical resection of all pathological tissue, with the additional use of other treatment modalities where required. These strategies are not (always) sufficient; there are high recurrence rates, especially for diffuse-type TGCT. In **Chapter 5,** a systematic review of the literature was presented, describing all known treatment options for TGCTs of large joints and their clinical results. Over the past century, progress has been limited. The available treatment options, which revealed varying success rates and morbidities, were surgical versus non-surgical, partial versus complete synovectomies, open versus arthroscopic synovectomies, radiosynovectomy, external beam radiotherapy, and target treatments. Furthermore, additional or self-contained treatments were also available, including cryosurgery, immunotherapy, arthroplasty, arthrodesis or amputation.

These various treatments have been proposed and applied to treat TGCT; however, due to the low incidence of the disease, randomised clinical trials are lacking and treatment efficacies are hard to compare. Treatment guidelines were established to improve the future comparability and aggregation capabilities of study results from different centres, as well as to support physicians in making the optimal treatment decisions. An international registry generated through existing networks would provide better insights into the outcomes of this disease; therefore, a key set of data was proposed for investigation and ideally incorporation into a registry.

The results of arthroplasty and cryosurgery were retrospectively investigated in more detail. **Chapter 6** described the outcomes of patients with TGCT who had

received a knee or hip arthroplasty for extended disease or osteoarthritis. It confirmed that arthroplasty is a treatment option after surgical synovectomy; however, disease recurrences, implant loosening and other complications do occur, even after years of follow up.

In **Chapter 7,** the results of cryosurgery in addition to surgical resection were described. This study confirmed the difficulty of research using small, retrospective, heterogeneous patient groups. Cryosurgery may serve as an additional treatment for diffuse TCGT in selected cases; however, the presented study did not find an advantage for additional cryosurgery over surgical resection except in the reduction of recurrences.

Diffuse-type TGCT often causes significant morbidity due to local recurrences necessitating multiple surgeries. Targeted therapy, if effective and with acceptable toxicities, might prevent surgery with unacceptable morbidity risk or permit less invasive surgeries in a neoadjuvant setting. TGCTs are CSF-1-driven proliferative disorders; therefore, the international multi-institutional retrospective study presented in **chapter 8** was performed to investigate the long-term effects of using imatinib mesylate, a CSF-1R blocker, for patients with locally advanced and recurrent diffuse-type TGCT. In the patients who benefitted from the imatinib mesylate treatment, a prolonged activity on TGCT symptoms was confirmed, even after the discontinuation of the treatment; however, high rates of treatment interruption and additional treatments were also recorded.

TGCT can affect any synovial joint and can rarely occur in the temporomandibular joint. The management of TGCT in the temporomandibular joint is similar to treating the disease in the large joints, requiring a complete synovectomy to remove all pathologic tissue, combined with other treatment modalities when required. The location of the temporomandibular joint can mean that the complete removal of TGCTs in this region has unacceptable morbidity rates in terms of a mutilating surgery however, and the effect of multimodal treatment(s) is unknown. **Chapter 9** reported the results of three cases with TGCT of the temporomandibular joint, and a review of the relevant literature was presented. TGCT of the temporomandibular joint is diagnosed using MRI, with additional CT if necessary to evaluate the extent of disease. When in doubt, an open biopsy might be necessary to confirm the diagnosis. The treatment for the localised-type disease is an excision biopsy, while treatments for diffuse-type disease should be individualised depending on the patient age, symptom severity, extent of disease and progression, expected mutilation of surgical interference, and current systemic treatment options. In stable disease, a 'wait and see' policy is a viable option. Additional treatments should be reserved for symptomatic, irresectable tumours or residual disease after surgical treatment and or persistent complaints.

## Outcome

**Chapter 10** described the long-term follow-up of a single institution's large consecutive series of patients with TGCTs in large joints. The mean age at the time of diagnosis was 37.5 (range: 17.2–71.7) years and 33.9 (range: 14.4–62.2) years for localised- and diffuse-type TGCT, respectively. The knees were most commonly affected (88% of patients). The treatments received were surgery, external beam radiation therapy, radiosynovectomy, systemic therapy, immunotherapy or combinations of treatments. A total of 49 patients (46%) had received prior treatment elsewhere. The mean follow-up time from diagnosis until last contact was 7.0 (range: 0.3–27.4) years for localised-type TGCTs and 14.5 (range: 1.1–48.7) years for diffuse-type TGCT of the knee. The recurrence rates of TGCT deteriorated with time, particularly for the diffuse-type disease; for the knee, the one- and five-year recurrence-free survival (RFS) rates were 69% and 32%, respectively. Long follow-up times confirmed that diffuse-type TGCT is often a continually recurring problem, and over time it becomes increasingly difficult to cure.

Besides recurrences and RFS rates, the QoL and functional scores are critical endpoints in demonstrating the clinical relevance and impact of treatments for benign diseases in which death is not an outcome variable. **Chapter 11** describes the largest prospective cohort, including the longest follow-up time, to report on patient-reported outcome measures (PROMs) in therapy-naïve patients with localised- and diffuse-type TGCTs in large joints. For both TGCT subtypes, patient QoL (SF-36) was significantly and clinically relevantly decreased before the surgical treatment, including on the main physical domains and some mental domains, in comparison with the general population means. Three-to-six months post-operatively, all SF-36 subscales improved to the level of the general population means and continued to be fairly stable over the following years. The pain experience (VAS) in both subtypes differed tremendously between patients and over time. The mean function (WOMAC) scores for pain, stiffness and physical functioning in both TGCT subtypes revealed no clinically relevant differences in patients before (baseline) and after their surgery; however, in patients with diffuse-type TGCT, the WOMAC pain and physical function scores showed a trend of improvement postoperatively, for up to five years of follow-up. These findings showed that patients with TGCT need three to six months after surgery to recover to a QoL similar to the general population mean. Joint function improvement showed a similar trend, although the results lacked clinical relevance. Surgery had no influence on the pain experienced, confirming the importance of surgery as a treatment for TGCT.

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# 13

# Discussion and future perspectives

# Discussion

TGCT is a rare proliferative joint disease, mostly affecting young adults, and often causes significant morbidity due to local recurrences necessitating multiple surgeries. Adding to and improving the knowledge about rare diseases is a great challenge, and the existing literature yields mostly small retrospective case series. The research presented in this thesis clarifies some aspects of TGCT.

## Standardisation of TGCT subtypes is essential

TGCT is more common than previously believed **(chapter 2),** but it is still rare. To increase patient numbers in studies of TGCT, the two forms, localised-(extremity) and diffuse-type, are often merged,[4,35,44,50,74,121,122] despite the decades-long consensus that these two entities behave biologically differently.[2] Making a clinical distinction between localised- and diffuse-type TGCTs can be difficult, especially for clinicians not familiar with this rare disease.[51] A recent Danish registry-based TGCT study on incidence,[269] published roughly at the same time as the pathology-based incidence study presented in this thesis **(chapter 2),** confirmed the difficulty of diagnosing and categorising TGCT subtypes. Both studies used different subtype definitions, despite the efforts of the WHO to uniformly classify TGCT[1], and came up with different incidence rates.

Localised TGCT of digits (localised-digits) were analysed as a distinct entity to the other localised-type TGCTs **(chapter 2)**, because the majority of lesions localised to joints distal to the metacarpal or metatarsal bones arise from the tendon sheath and less frequently from the synovial lining of the digital joints. In our opinion and that of others, localised-digits TGCT is a distinct subtype within the same disease spectrum.[74,75] The Danish registry-based TGCT study included patients with TGCT of the digits, who comprised over half of their patients with localised-type TGCTs. Even when all patients with TGCT (localised-digits, localised extremity and diffuse-type) were combined in the present study, the incidence of TGCT (worldwide incidence rate: 43 per million person-years) found here **(chapter 2)** differs a little from that of Denmark (39 per million person-years).[18,269]

Even if the different subtypes were always classified in the same way, the presented 'severity classification' **(chapter 4)** suggests that subdividing between localised-extremity and diffuse-type TGCTs is an oversimplification, and fails to estimate the differences in recurrence rates for individual patients. There is a difference in the risk of developing recurrent disease between mild-localised, severe-localised, moderate-diffuse and severe-diffuse forms of TGCT, with the latter behaving the most aggressively.

In contrast to other studies,[4,162] we found that females showed a slight predisposition to both types of TGCT (male:female ratio 1:1.5) **(chapter 2)**, in accordance

with the preliminary results of an international retrospective registry study with over 2,000 patients (abstract for EMSOS 2018).[266] Ehrenstein et al. confirmed this slight predisposition of females (61%) for localised-type TGCTs, but reported an equal sex prevalence (females 51%) in diffuse-type TGCT patients.

## Influence of anatomical locations on tumour behaviour

The anatomic site of TGCT may have significant influence on its clinical behaviour;[2,8,59] however, whether this variation in behaviour is caused by the location itself or by the existence of undefined subtypes is unknown. According to Chung et al.,[58] bone invasion is more likely to occur in joints without large synovial recesses to accommodate the expanding synovial masses, such as the hip. Furthermore, because of the deeper location, the diagnosis of TGCTs in this region may be delayed. Schwartz et al.[50] found higher recurrence rates in affected knees than any other location. In **chapter 6**, which described arthroplasties for patients with TGCTs, patients with affected hips received a prosthesis over 20 years earlier than patients with TGCT of the knee. This might be caused by a higher incidence of bone erosions and cyst formation in TGCT hips compared to knees. Nevertheless, all locations are combined in most outcome measurements to increase patient numbers.[3,19,44,50,75,120]

In contrast, other studies did not show a (significant) difference in recurrence rates for both localised- and diffuse-type TGCTs when comparing the knee with other joints.[37,38,75,111] In this thesis, all large joints (including the knees, hips and ankles) were included to sub-classify the disease severity of TGCT **(chapter 4)**, to investigate efficacy of imatinib mesylate **(chapter 8)**, and for measurements of patient-reported outcomes **(chapter 11)**. The presented incidence study of this thesis **(chapter 2)** showed a predominance for the knee joint in adult patients with localised- (46%) and diffuse-type (64%) TGCTs, in line with the affected joints in children **(chapter 3)** and those of the patients presented in the long-term follow-up study **(chapter 10)**. The preliminary results of the international retrospective registry study with over 2,000 patients revealed no effect of TGCT location on the risk of developing recurrent disease.[266]

## Heterogeneously treated patients

There is a large diversity in the treatment options for TGCT; in most case series, more than three different treatments are described.[3,19,44,50,54,75,117] If the already relatively heterogeneous patients were further divided into the different treatment groups, the groups would be too small to draw adequate conclusions. To minimise heterogeneity in patients and treatments, only patients primarily treated with open synovectomies were included in the TGCT severity classification study **(chapter 4)**. In **chapters 6, 7 and 8,** the heterogeneity of prior treatments was a

limitation. The presented long-term follow-up results of this thesis **(chapter 10)** therefore included detailed information on each patient, which will enable future reviews to better analyse subsets of patients who received specific treatments.

In the assessment of treatments, patient groups consist of newly diagnosed patients (therapy-naïve) and patients already treated elsewhere.[5,19,41,50,51] Some studies focus on this topic and describe the treatments that patients received before arrival in their centre,[19,50,51,55] while others do not report the composition of their patient groups at all.[3,44] This leads to bias in outcome measurements, such as the overall recurrence rates, which appear higher than they really are in comparison with case series comprising only therapy-naïve cases. Schwartz et al.[50] described this manipulation as referral bias, which is mostly present in patient populations from tertiary centres. They showed that patients who had received previous treatment had more recurrences than therapy-naïve patients ($p < 0.01$); however, the patients with previous procedures had unusual cases of TGCT. Their prior operations may have affected the disease recurrence in some way, or their disease may have had biologically aggressive characteristics or been located in joints less amenable to surgical eradication. The presented long-term follow-up results **(chapter 10)** and the preliminary results of an international retrospective registry study with over 2,000 patients (abstract for EMSOS 2018)[266] confirmed that patients with TGCT do worse when they have already been treated elsewhere.

By studying the incidence rates of TGCT **(chapter 2),** it was discovered that Dutch referral centres only treat 'the tip of the iceberg'; only 18% of diffuse-type TGCTs were primarily treated in one of the four tertiary orthopaedic oncology centres. This might be the case worldwide, and must therefore be kept in mind when interpreting research results. It is likely that only the referral centres only treat the worst patients, who would also be most prone to develop recurrent disease. Most of the centres involved in the international retrospective study of over 2,000 patients were tertiary referral centres,[266] meaning that even a study involving a large number of patients with a rare disease might have a significant patient selection bias that should be taken into account when considering the results of this study. For now, however, these data represent the best information available. Furthermore, most patients underwent surgery as a first treatment, the results of which are dependent on surgeon experience.

In patients with locally advanced or recurrent TGCTs, systemic therapies targeting the CSF-1/CSF-1R axis have been investigated (nilotinib, imatinib, pexidartinib (PLX3397), emactuzumab (RG7155) and cabiralizumab (FPA008)). Some of these systemic treatments have been studied and proven effective,[63,64] while novel and more potent agents are still under investigation.[16,66,255] Patients included in these trials, as well as those in the international long-term follow-up study of imatinib mesylate **(chapter 8)**, were very heterogeneous. Strict patient

selection for trial inclusion is desirable to accurately evaluate the effect of these treatments; however, patient selection for trial inclusion is currently decided by the preferences of the treating physician and might differ between centres. Also, the inclusion criteria differ between countries, depending on the availability and reimbursement of drugs and the availability of clinical trials. Using the MRI-based severity classification **(chapter 4)**, more aggressive TGCT subtypes were defined in an attempt to include more uniformly defined patients in future clinical trials. Also, the evaluation of the effect of treatments would benefit from clear agreements about response monitoring.

## Heterogeneous outcome measures

Some studies used various outcome measures, including recurrence rates, RFS percentages, numbers of secondary osteoarthritis and the rate of complications, while others used only broad outcome terms (good, excellent, fair, poor, etc.). Unfortunately, the largest case series (> 20 patients) used different outcome measures or provided incomplete descriptions.[76] In our study of the long-term follow-up results **(chapter 10)**, the recurrence rates, RFS percentages and complications were described, in addition to the QoL (SF-36). Ideally, SF-36 values should be corrected for age; however, because of the small number of patients and the presence of treatment bias, this was not applied. In **chapter 11**, data were collected from consecutive patients for years, but the number of patients was still relatively small for demonstrating a clinically relevant and/or significant treatment effect on HRQoL and joint function. This might be explained by (1) high levels of variability in the HRQoL and joint function results, (2) a small effect of surgery on HRQoL and joint function, (3) the use of patient outcome measures (SF-36, VAS and WOMAC) that were not sensitive enough to measure HRQoL and joint function in TGCT. These patient outcome measures are broadly used to assess diseases such as osteoarthritis and their treatment effects.[258,264] After recurrence rates, QoL and joint function are the most important measures to quantify and compare the treatment effects on patients with TGCT.

## Definition of recurrent disease

Some studies accept clinical symptoms and radiographs to detect recurrent disease,[3,5] while others insist on MRI or even histological confirmation before designating a relapse, and only a few studies differentiated between residual disease and recurrences.[19,117] Again, a decision needs to be made about whether clinical symptoms are considered sufficient evidence for recurrent disease, or whether MRI and histological confirmations are needed. What are the treatment implications of residual or recurrent disease detected using MRI in the absence of clinical symptoms? Should additional treatment(s) occur, or is a conservative 'wait

and see' approach sufficient? The incidence study of this thesis **(chapter 2)** was pathology-based, and patients with TGCT were not represented if they had not undergone a biopsy or treatment. As a result, both the incidence and recurrence rates are likely underestimated.

Further, a clear differentiation between true recurrent disease and operations for other reasons is essential. Not all operations in the same joint indicate recurrent TGCT, as they are frequently performed for secondary osteoarthritis requiring arthroplasty or stiffness requiring manipulation under anaesthesia. After arthroplasty, diagnoses of recurrent disease can be challenging because of MRI artefacts caused by the prostheses themselves. Recurrent disease could be suspected from clinical complaints in combination with ultrasonography; however, only histopathology could confirm recurrent disease.

Finally, TGCT can recur after many years; therefore, the follow-up times used in many studies are often too short.[59] Due to the retrospective character of these studies, data are missing and contact is lost with many patients. The long-term follow-up study presented in this thesis **(chapter 10)** confirms the importance of reporting the time at which outcome measures such as recurrence rates and RFS rates were evaluated; the recurrence rates increased over time, making studies of these rates without indications of the time relatively useless.

## Future perspectives

The most severely affected patients, with the highest risk of morbidity due to extended disease and/or multiple recurrences, are also the most in need of effective treatment(s). Efforts should be made to identify these patients (with the biologically aggressive subgroup of TGCTs) using radiological, clinical, histopathological and molecular approaches. The MRI severity classification presented in this thesis **(chapter 4)** may be a good start, but it requires further investigation and fine-tuning. Relationships between radiology imaging and clinical symptoms, such as the locations of the initial TGCT, growth of recurrences and osteoarthritis, might be of great importance.

The role of systemic treatment in TGCT requires further exploration. The patients who would benefit most from systemic therapy should be identified based on molecular tumour features sensitive to that specific treatment. Subsequently, an optimal treatment strategy should be developed. The combination of a short treatment period with a durable effect after discontinuation should be pursued, as even minor toxicities mean it is challenging to maintain compliance for years. The use of CSF-1R inhibitors in the perioperative setting still requires further exploration. To prevent unnecessary systemic treatment, the development of local

treatments, such as intra-articular injections against TGCT that do not interfere with cartilage and have no systemic side effects, would be of major value.

The impact of TGCT and its treatments on QoL and joint function must be further defined. Specific TGCT patient-reported outcome measures should be developed to enhance the quantity and quality of the treatment effects, especially with the arrival of systemic treatments. It is vital that uniform time intervals are used for each patient and that objective joint-specific function measurements are explored. The chronic appearance of TGCT, particularly the diffuse type, in relatively young adults of working age will probably have an incredible impact on healthcare burden and costs; however, these aspects remain undefined and have not been subject of research.

Finally, given the rarity of the disease, randomised studies are not to be expected, but the establishment of an international registry (such as was initiated with the TGCT Observational Platform Project from Daiichi Sankyo) through existing networks would provide better insights into the outcomes of this disease. We therefore proposed a 'key outcome set' of data to be investigated and ideally reported in such a registry or in case series. This would allow case series from different centres to be compared and analysed together, resulting in a higher level of evidence for the optimal treatment of TGCT.

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## Nederlandse samenvatting

In dit proefschrift worden de incidentie, diagnostiek, behandelmogelijkheden en uitkomstparameters bij patiënten met een reusceltumor van de weke delen (Tenosynovial Giant Cell Tumour, TGCT) beschreven. In **hoofdstuk 1** wordt een overzicht van de huidige inzichten gegeven. TGCT is een zeldzame, goedaardige tumor uitgaande van gewrichtskapselslijmvlies, een peesschede of een slijmbeurs. Er zijn twee vormen bekend, namelijk de lokale vorm en de diffuse vorm, waarbij de lokale vorm nog verder onderverdeeld kan worden in TGCT in vingers en tenen of in de grote gewrichten (ofwel in ledematen proximaal van vingers en tenen zoals in de knie, de heup, de enkel etc.). Kennis over de incidentie van TGCT was voorheen gebaseerd op een onderzoek uit 1980 dat was verricht in één land (de Verenigde Staten). In dit Amerikaanse onderzoek werd een jaarlijkse incidentie van 9 per 1.000.000 mensen (de lokale vorm) en 2 per 1.000.000 mensen (de diffuse vorm) gevonden.

## Incidentie

In **hoofdstuk 2** wordt een nationale studie gepresenteerd die verricht is in Nederland. Hierin zijn gegevens gebruikt uit het Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA) die een periode van vijf jaar bestrijken. Op basis hiervan zijn mondiale incidentiecijfers berekend voor de lokale vorm in de vingers en tenen, de lokale vorm in de grote gewrichten en de diffuse vorm. Deze zijn respectievelijk 29, 10 en 4 per 1.000.000 persoonsjaren. Dit betekent dat hoewel TGCT nog steeds valt onder de zeldzame aandoeningen (ziekte komt bij minder dan 1 op de 2000 mensen voor), uit deze resultaten blijkt dat de ziekte vaker voorkomt dan voorheen werd verondersteld. Beide vormen kwamen het vaakst voor in het kniegewricht, en traden iets vaker op bij vrouwen, namelijk anderhalf keer vaker dan bij mannen. Patiënten waren gemiddeld 47 jaar toen ze voor het eerst werden behandeld. Voor beide vormen geldt dat een open resectie de primaire behandeling was.

In **hoofdstuk 3** wordt een onderzoek gepresenteerd waarin een overzicht wordt gegeven van alle gegevens van pediatrische patiënten met TGCT die zijn gepubliceerd in de periode 1990-2016. In dit onderzoek zijn ook de gegevens van kinderen jonger dan 18 jaar uit de nationale studie naar de incidentie van TGCT, die eerder zijn gepresenteerd in **hoofdstuk 2,** opgenomen. Daarnaast werden klinische gegevens uit de periode 1995-2015 van TGCT bij kinderen in kaart gebracht met behulp van de nationale database van bot- en weke delen tumoren. Het genormaliseerde frequentiecijfer voor TGCT bij kinderen was 2,4 per 1.000.000 persoonsjaren (de lokale vorm, met uitzondering van vingers en tenen) en 1,1 per 1.000.000 persoonsjaren (de diffuse vorm). Zowel bij kinderen als volwassen bestonden de symptomen uit zwelling, pijn en een beperkte beweeglijkheid. De

diagnostische vertraging (d.w.z. de periode tussen het eerste artsenconsult en het moment waarop de diagnose werd gesteld) bedroeg gemiddeld 12 maanden (variërend van 1 tot 72 maanden). Er werden geen verschillen gevonden tussen kinderen en volwassenen wat betreft de geslachtsverhouding van de patiënten, symptomen, eerste behandeling, recidivering van de ziekte, follow-up status of gemiddelde duur van de follow-up.

## Diagnostiek

MRI is de meest onderscheidende beeldvormende techniek om de diagnose TGCT te stellen, de operatie technisch goed voor te bereiden (door de mate van uitbreiding van de ziekte in kaart te brengen) en de ziekte te evalueren tijdens de follow-up. Aan de hand van MRI-beelden kan de opvallende nodulaire proliferatie (bij de lokale vorm) of de villeuze proliferatie van het gewrichtskapselslijmvlies (bij de diffuse vorm) worden aangetoond. In het verleden zijn echter nog geen onderscheidende kenmerken gerapporteerd op basis waarvan de mate van tumoruitbreiding in relatie tot de klinische uitkomst kan worden beschreven of gekwantificeerd. Het is uit klinisch en wetenschappelijk oogpunt belangrijk dat MRI-beelden eenduidig worden beschreven. In **hoofdstuk 4** hebben vakinhoudelijke deskundigen daarom mogelijk onderscheidende MRI-parameters gedefinieerd om de mate van ziekte-uitbreiding te kunnen vaststellen. Tot deze parameters behoren het subtype van de ziekte, de mate waarin de gewrichten zijn aangedaan, de mate waarin het kraakbeen is aangedaan, en de betrokkenheid van spier-/peesweefsel, ligamenten of neurovasculaire structuren. Deze parameters werden aan de hand van twee verschillende studiepopulaties geëvalueerd, met uitzondering van betrokkenheid van het kraakbeen en neurovasculaire structuren. Zo werden vier subgroepen onderscheiden met ieder een verschillende mate van ernst van de ziekte, waarbij ernst werd gedefinieerd op basis van het recidiefrisico. Op basis van de voorgestelde classificatie krijgen artsen en patiënten informatie over de mate van ziekte-uitbreiding en het recidiefrisico na operatief ingrijpen. Door de patiënten op deze manier in te delen, kunnen degenen met de ernstigste vorm (d.w.z. degenen met het hoogste recidiefrisico) worden geïdentificeerd. Dit is belangrijk omdat zij in aanmerking komen voor andere dan standaardbehandelingen. Bovendien is het relevant omdat behandelingen in een dergelijke, meer homogene, risicogroep op deze manier beter geëvalueerd kunnen worden.

## Behandelingen

Momenteel bestaat de behandeling van TGCT uit het operatief verwijderen van al het aangedane weefsel, zo nodig aangevuld met andere behandelingen. Deze aanpak is niet (altijd) afdoende. Het recidiefrisico is hoog, vooral bij de diffuse vorm. In **hoofdstuk 5** wordt een systematisch literatuuroverzicht gepresenteerd. Hierin worden alle bekende behandelmethoden voor TGCT in de grote gewrichten en de klinische resultaten van deze behandelingen beschreven. De afgelopen eeuw is slechts weinig vooruitgang geboekt. De behandelopties die voorhanden waren, hadden wisselend succes en leidden in wisselende mate tot morbiditeit. Deze behandelingen waren een partiële of complete synovectomie (wegsnijden van het gewrichtskapselslijmvlies), een open of arthroscopische synovectomie, radiosynovectomie, externe beam radiotherapie (uitwendige bestraling) en systemische behandelingen met doelgerichte medicatie Daarnaast waren er ook aanvullende of op zichzelf staande behandelingen, waaronder cryochirurgie, immunotherapie, artroplastiek (gewricht vervangen voor een prothese), artrodese (aangedaan weefsel verwijderen en het gewricht vastzetten) of amputatie.

Al deze verschillende behandelingen zijn toegepast bij TGCT. Vanwege de lage incidentie van de ziekte zijn er echter geen gerandomiseerde klinische trials uitgevoerd en is het moeilijk om de behandelingen met elkaar te vergelijken wat betreft de mate van effectiviteit. Er werden behandelrichtlijnen opgesteld om toekomstige studieresultaten van verschillende centra beter met elkaar te kunnen vergelijken en samenvoegen, en om artsen te helpen de beste behandeling te kiezen. Een internationaal register zou meer inzicht kunnen geven in de uitkomsten van deze ziekte. Daarom werd voorgesteld van alle TGCT patiënten dezelfde basisgegevens bij te houden voor onderzoek en om - in het ideale geval - op te nemen in een internationaal register.

De resultaten van artroplastiek en cryochirurgie zijn retrospectief meer in detail onderzocht. In **hoofdstuk 6** worden de uitkomsten van patiënten met TGCT beschreven bij wie een knie- of heupprothese werd geplaatst vanwege een uitgebreide vorm van de ziekte of artrose. Aan de hand van deze uitkomsten werd bevestigd dat artroplastiek succesvol kan worden toegepast na een operatieve synovectomie. Hierbij dient opgemerkt te worden dat recidivering van de ziekte, het losraken van de prothese en andere complicaties zich zelfs na jaren follow-up nog kunnen voordoen.

In **hoofdstuk 7** worden de resultaten van cryochirurgie als aanvulling op het chirurgisch verwijderen van de tumor beschreven. Deze studie onderstreept de beperkingen van het verrichten van onderzoek met kleine, retrospectieve en heterogene patiëntgroepen. Cryochirurgie kan in geselecteerde gevallen dienen als aanvullende behandeling voor de diffuse vorm van TCGT. Toch kwam uit de

gepresenteerde studie geen voordeel naar voren van additionele cryochirurgie ten opzichte van het enkel chirurgisch verwijderen van tumorweefsel, behalve wat betreft het verminderen van het aantal recidieven.

De diffuse vorm veroorzaakt vaak aanzienlijke morbiditeit vanwege lokale recidieven met als consequentie meerdere operaties ter behandeling hiervan. Systemische behandeling in de vorm van doelgerichte therapie, mits effectief en met een acceptabele mate van toxiciteit, kan een operatie met een onacceptabele kans op morbiditeit voorkomen of leiden tot minder invasieve operaties. TGCT is een proliferatieve aandoening met een verhoogde expressie van het gen voor colony-stimulating factor 1 (CSF-1). In **hoofdstuk 8** wordt een internationale retrospectieve multicenter studie gepresenteerd met als doel het langetermijn-effect van het gebruik van imatinib, een medicijn dat o.a. CSF1R remt, te onderzoeken bij patiënten met TGCT in lokaal gevorderde en recidiverende diffuse vorm. Bij patiënten die baat hadden bij de behandeling met imatinib werd een langdurig effect op de ziektesymptomen waargenomen, zelfs na het stoppen van de behandeling. De behandeling werd echter vaak onderbroken, bijvoorbeeld i.v.m. bijwerkingen, en er werden ook vaak andere behandelingen achteraf gegeven.

TGCT kan voorkomen in elk synoviaal gewricht, soms ook in het kaakgewricht. De aanpak van TGCT in het kaakgewricht is vergelijkbaar met die van TGCT in de grote gewrichten. Al het aangedane weefsel dient te worden verwijderd met een complete synovectomie, zo nodig gecombineerd met andere behandelingen. Vanwege de locatie van het kaakgewricht kan het volledig verwijderen van TGCT weefsel leiden tot onacceptabele morbiditeit in de vorm van verminking. Daarnaast is het effect van multimodale behandeling(en) onbekend. In **hoofdstuk 9** worden de resultaten van drie gevallen met TGCT in het kaakgewricht gepresenteerd. Daarnaast werd een overzicht van de relevante literatuur gegeven. De diagnose TGCT in het kaakgewricht wordt gesteld met behulp van MRI, zo nodig aangevuld met een CT-scan om de mate van ziekte-uitbreiding in kaart te brengen. Bij twijfel kan het noodzakelijk zijn een biopt te nemen om de diagnose te bevestigen. De behandeling van de lokale vorm bestaat uit een excisiebiopt. De behandeling van de diffuse vorm dient afgestemd te worden op basis van de leeftijd van de patiënt, de ernst van de symptomen, de mate van ziekte-uitbreiding en voortgang, de verwachte mate van verminking als gevolg van operatief ingrijpen en de huidige systemische behandelmogelijkheden. Indien de ziekte stabiel is, is een afwachtend beleid een reële optie. Aanvullende behandelingen moeten alleen worden toegepast bij tumoren die symptomen veroorzaken en niet chirurgisch kunnen worden verwijderd of bij resttumor na het operatief verwijderen en/of aanhoudende klachten.

## Uitkomsten

In **hoofdstuk 10** wordt de lange termijn follow-up van een grote serie van opeenvolgende patiënten (N=107) met TGCT in de grote gewrichten binnen één instelling beschreven. Op het moment waarop de diagnose werd gesteld, was de gemiddelde leeftijd van de patiënten met de lokale vorm 37,5 jaar (variërend van 17,2 tot 71,7 jaar). De gemiddelde leeftijd van de patiënten met de diffuse vorm was op het moment waarop de diagnose werd gesteld 33,9 jaar (variërend van 14,4 tot 62,2 jaar). De knieën waren het vaakst aangedaan (dit gold voor 88% van de patiënten). De volgende behandelingen werden toegepast: chirurgie, uitwendige bestraling, radiosynovectomie, systemische therapie, immunotherapie of combinatiebehandelingen. In totaal hadden 49 patiënten (46%) al elders therapie ondergaan. De gemiddelde duur van follow-up vanaf het moment waarop de diagnose werd gesteld tot het laatste contact bedroeg 7,0 jaar (variërend van 0,3 tot 27,4 jaar) bij patiënten met de lokale vorm en 14,5 jaar (variërend van 1,1 tot 48,7 jaar) bij patiënten met de diffuse vorm in de knie. Het recidiefrisico van met name de diffuse vorm nam na verloop van tijd toe. De recidiefvrije overleving na één en vijf jaar voor TGCT in de knie bedroegen respectievelijk 69% en 32%. Tijdens lange follow-up perioden bleek dat de diffuse vorm vaak een terugkerend probleem is, en dat patiënten met deze vorm na verloop van tijd steeds moeilijker kunnen worden genezen.

Naast recidivering van de ziekte en recidiefvrije overleving vormen ook de kwaliteit van leven en functionele scores belangrijke eindpunten. Hiermee worden de klinische relevantie en het effect van behandelingen aangetoond bij goedaardige ziekten waarbij de dood geen uitkomstvariabele is. In **hoofdstuk 11** wordt de grootste prospectieve cohortstudie met de langste follow-up periode naar patiënt gerapporteerde uitkomstmaten (patient-reported outcome measures, PROMs) beschreven bij therapie-naïeve patiënten (primaire patiënten zonder eerdere behandelingen) met de lokale en diffuse vorm van TGCT in de grote gewrichten. Bij beide subtypen van de ziekte was de kwaliteit van leven van patiënten (gemeten met de SF-36 vragenlijst) significant en klinisch relevant afgenomen voorafgaand aan operatief ingrijpen in vergelijking met de gemiddelde waarden voor de algemene bevolking. Dit gold ook voor de voornaamste fysieke domeinen en een aantal psychische domeinen. Drie tot zes maanden na de operatie waren de scores voor alle sub-schalen van de SF-36 weer op hetzelfde niveau als de gemiddelde waarden voor de algemene Nederlandse bevolking. In de daaropvolgende jaren bleven de scores vrij constant. Voor beide vormen gold dat er enorme verschillen bestonden, zowel tussen patiënten onderling als na verloop van tijd, wat betreft ervaren mate van pijn (gemeten met de VAS-score). De gemiddelde functiescores volgens WOMAC voor pijn, stijfheid en fysiek functioneren toonden voor geen van

beide vormen klinisch relevante verschillen bij patiënten vóór (baseline) en na de operatie. Bij patiënten met de diffuse vorm verbeterden de WOMAC-scores voor pijn en fysiek functioneren echter wel na de operatie. Deze trend was tot vijf jaar na de operatie waarneembaar. Uit deze bevindingen blijkt dat initieel therapie-naïeve patiënten met TGCT drie tot zes maanden na de operatie weer dezelfde kwaliteit van leven ervaren als de algemene Nederlandse bevolking. Ook de gewrichtsfunctie verbeterde significant drie tot zes maanden na de operatie, maar deze resultaten waren niet klinisch relevant. Operatief ingrijpen had geen effect op de mate van ervaren pijn. Dit onderstreept het belang van chirurgie als behandeling voor therapie-naïeve TGCT patiënten. Patiënt gerapporteerde uitkomstmaten voor patiënten met uitgebreide- of recidiefziekte zijn nog niet onderzocht. Het is te verwachten dat deze patiënten minder baat hebben bij alleen chirurgische behandeling.

# 14

# 15

# Appendices

# Abbreviations

ACL= anterior cruciate ligament
AWD= alive with disease
BIG= Bone impaction grafting
CBS= central bureau of statistics
CI= confidence interval
CIS20r= 20-item checklist individual strength questionnaire
CME= institutional review board
CML= chronic myeloid leukaemia
CR= Cruciate retaining
CSF-1= colony stimulating factor 1
CSF-1R= colony stimulating factor 1 receptor
CT= computed tomography
D-PVNS= diffuse pigmented villonodular synovitis
DTGCT= diffuse tenosynovial giant cell tumour
Dt-GCT= diffuse tenosynovial giant cell tumour
EBRT= external beam radiation therapy
FPA008= cabiralizumab
GBA= gemeentelijke basis administratie
GCT-TS= giant cell tumour of the tendon sheath
GIST= gastrointestinal stromal tumours
GRE= gradient echo
HHS= harris hip score
HP= hemi arthroplasty knee
HR=hazard Ratios
ID= patient identification
IM= imatinib mesylate
IQR= inter quartile range
IR= incidence rate
KSS= knee society score
L-PVNS= localized pigmented villonodular synovitis
LTGCT= localized tenosynovial giant cell tumour
Lt-GCT= localized tenosynovial giant cell tumour
ME= partial meniscectomy
Mo= months
MRI= magnetic resonance imaging
MSTS= musculoskeletal tumor society
MUA= manipulation of the knee under anesthesia
N= number of patients
NA= not available
NED= no evidence of disease
OSM= osteosynthesis material

SD= standard deviation
SE= surgical synovectomy
SF36= 36-item short form health survey
SPSS®= statistical package for social sciences statistics
SVP= synovitis (villo)nodularis pigmentosa
PALGA= pathologisch-anatomisch landelijk geautomatiseerd archief (Dutch pathology registry)
PCL= posterior cruciate ligament
PET= FDG-positron emission tomography
PF= patella femoral arthroplasty
PFC= patella femoral component
PLX3397= pexidartinib
PFS= progression-free survival
PS = posterior stabilized
PVNS= pigmented villonodular synovitis
QoL =quality of life
RG7155= emactuzumab
ROM= range of motion
RT= external beam radiation therapy
THA= total hip arthroplasty
TGCT= tenosynovial giant cell tumours
TKA= total knee arthroplasty
TMJ= temporomandibular joint
TNF= tumour necrosis factor
TTF= time to treatment failure
WHO= World Health Organization
WOMAC= Western Ontario and McMaster Universities osteoarthritis index
yrs= years

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MJL Mastboom, E Palmerini, **FGM Verspoor**, AJ Rueten-Budde, S Stacchiotti, EL Staals, G Schaap, PC Jutte, W Aston, H Gelderblom, A Leithner, D Dammerer, A Takeuchi, Q Thio, X Niu, J Wunder, TGCT-study group & MAJ van de Sande. Treatment outcome in largest patient population of diffuse-type tenosynovial giant cell tumours. A multicentre-pooled database of 31 international sarcoma centres. 2018; submitted.

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*These authors contributed equally to this work

# Curriculum vitae

Floortje Gertrude Maria Verspoor was born on 20th November, 1980, in Nijmegen, the Netherlands. She grew up with five sisters and loved to play all kind of sports, particularly handball, which she played in the Dutch national youth team. She graduated high school (VWO, Montessori college, Nijmegen) in 1999. During her studies in Biomedical Health Sciences and Medicine at the Radboud UMC in Nijmegen she worked abroad. In the United States, she undertook a scientific internship on acute myeloid leukaemia and myelodysplastic syndrome as part of her pathobiology major (Rush-Presbyterian-St. Luke's Medical Center in Chicago, 2003), and did a 'developing country' rotation in Tanzania as part of her Medicine degree (Sumve Designated District Hospital, 2007). She also performed research on the role of p-glycoprotein in apoptosis after cold preservation for her toxicology major (Department of Pharmacology-Toxicology, Radboud UMC in Nijmegen, 2002). In 2004, she obtained her MSc in Biomedical Health Sciences, followed by her MD in Medicine in 2007.

She performed research in haematology (initiating the registration of patients with ´myelodysplastic syndrome´ in the eastern Netherlands and research into the effect of lymphocyte injections in patients with chronic lymphocytic leukaemia, Radboud UMC in Nijmegen, 2004–2005), general surgery (Sentinel node biopsy in a cohort of 944 patients with cutaneous melanomas: significant or useless? Rijnstate hospital in Arnhem, 2006–2008), cardio-thoracic surgery (Delays in diagnostics and treatment of cardiac tumours are unacceptable. Radboud UMC in Nijmegen, 2009) and orthopaedics (pigmented villonodular synovitis, later tenosynovial giant cell tumours, Radboud UMC in Nijmegen, 2011–2018).

She completed her residency in general surgery (2011–2012) at the Rijnstate hospital in Arnhem and did her orthopaedic training (2012–2018) at the Rijnstate hospital in Arnhem , the sint Maartenskliniek and the Radboud UMC in Nijmegen. Her research led to this thesis on tenosynovial giant cell tumours at the Radboud UMC in Nijmegen (2011–today), later in collaboration with the Leiden UMC in Leiden (2016–today). She will complete her orthopaedic residency in December 2018, after which she will further specialise in oncological orthopaedics at the Amsterdam UMC as a fellow.

She lives with Bastiaan G. W. Derks and their sons Tigo C. Derks (born on 16th December, 2012) and Mischa J. Derks (born on 23rd April, 2014).